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<div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>			
(57) Abstract			
<p>The present invention relates to novel hypolipidemic, antihyperglycemic, antiobesity and hypocholesterolemic compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them. More particularly, the present invention relates to novel <math>\beta</math>-aryl-<math>\alpha</math>-oxysubstituted alkylcarboxylic acids of general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them.</p>			

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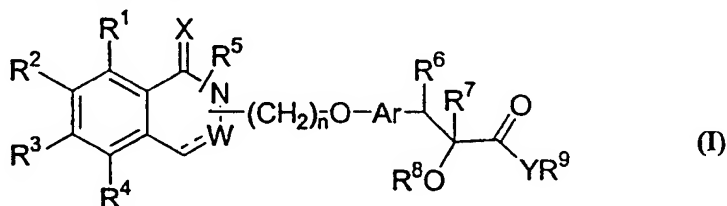
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**NOVEL ALKANOIC ACIDS AND THEIR USE IN MEDICINE, PROCESS  
FOR THEIR PREPARATION AND PHARMACEUTICAL  
COMPOSITIONS CONTAINING THEM**

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**Field of the Invention**

The present invention relates to novel hypolipidemic, antihyperglycemic, antiobesity and hypocholesterolemic compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them. More particularly, the present invention relates to novel  $\beta$ -aryl- $\alpha$ -oxysubstituted alkylcarboxylic acids of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them.



The present invention also relates to a process for the preparation of the above said novel compounds, their analogs, their derivatives, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

The present invention also relates to novel intermediates, processes for their preparation and their use in the preparation of compounds of formula (I).

The compounds of the present invention lower total cholesterol (TC); increase high density lipoprotein (HDL) and decrease low density lipoprotein (LDL), which have beneficial effects on coronary heart disease and atherosclerosis.

The compounds of general formula (I) are useful in reducing body weight and for the treatment and / or prophylaxis of diseases such as hypertension, coronary heart

disease, atherosclerosis, stroke, peripheral vascular diseases and related disorders. These compounds are useful for the treatment of familial hypercholesterolemia, hypertriglyceridemia, lowering of atherogenic lipoproteins, VLDL and LDL. The compounds of the present invention can be used for the treatment of certain renal  
5 diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy and nephropathy. The compounds of general formula (I) are also useful for the treatment and/or prophylaxis of insulin resistance (type II diabetes), leptin resistance, impaired glucose tolerance, dyslipidemia and disorders related to syndrome X such as hypertension, obesity, insulin resistance,  
10 coronary heart disease, and other cardiovascular disorders. These compounds may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and for the treatment of  
15 cancer. The compounds of the present inventions are useful in the treatment and/or prophylaxis of the above said diseases in combination / concomittant with one or more HMG CoA reductase inhibitors, hypolipidemic / hypolipoproteinemic agents such as fibric acid derivatives, nicotinic acid, cholestyramine, colestipol, probucol.

20

### Background of Invention

Atherosclerosis and other peripheral vascular diseases are the major causes affecting the quality of life of millions of people. Therefore, considerable attention has been directed towards understanding the etiology of hypercholesterolemia and  
25 hyperlipidemia and development of effective therapeutic strategies.

Hypercholesterolemia has been defined as plasma cholesterol level that exceeds an arbitrarily defined value called "normal" level. Recently, it has been accepted that "ideal" plasma levels of cholesterol are much below the "normal" level of cholesterol in  
30 general population and the risk of coronary artery disease (CAD) increases as cholesterol level rises above the "optimum" (or "ideal") value. There is clearly a definite cause and effect-relationship between hypercholesterolemia and CAD,



particularly for individuals with multiple risk factors. Most of the cholesterol is present in the esterified forms with various lipoproteins such as Low density lipoprotein (LDL), Intermediate density lipoprotein (IDL), High density lipoprotein (HDL) and partially as Very low density lipoprotein (VLDL). Studies clearly indicate that there is an inverse correlation between CAD and atherosclerosis with serum HDL-cholesterol concentrations. (Stampfer *et al.*, *N. Engl. J. Med.*, 325 (1991), 373-381) and the risk of CAD increases with increasing levels of LDL and VLDL.

In CAD, generally "fatty streaks" in carotid, coronary and cerebral arteries, are found which are primarily free and esterified cholesterol. Miller *et al.*, (*Br. Med. J.*, 282 (1981), 1741 - 1744) have shown that increase in HDL-particles may decrease the number of sites of stenosis in coronary arteries of human, and high level of HDL-cholesterol may protect against the progression of atherosclerosis. Picardo *et al.*, (*Arteriosclerosis* 6 (1986) 434 - 441) have shown by *in vitro* experiment that HDL is capable of removing cholesterol from cells. They suggest that HDL may deplete tissues of excess free cholesterol and transfer it to the liver (Macikinnon *et al.*, *J. Biol. Chem.* 261 (1986), 2548 - 2552). Therefore, agents that increase HDL cholesterol would have therapeutic significance for the treatment of hypercholesterolemia and coronary heart diseases (CHD).

20

Obesity is a disease highly prevalent in affluent societies and in the developing world and is a major cause of morbidity and mortality. It is a state of excess body fat accumulation. The causes of obesity are unclear. It is believed to be of genetic origin or promoted by an interaction between the genotype and environment. Irrespective of the cause, the result is fat deposition due to imbalance between the energy intake versus energy expenditure. Dieting, exercise and appetite suppression have been a part of obesity treatment. There is a need for efficient therapy to fight this disease since it may lead to coronary heart disease, diabetes, stroke, hyperlipidemia, gout, osteoarthritis, reduced fertility and many other psychological and social problems.

30

Diabetes and insulin resistance is yet another disease which severely effects the quality of life of a large population in the world. Insulin resistance is the diminished

ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistance, the body secretes abnormally high amounts of insulin to compensate for this defect; failing which, the plasma glucose concentration inevitably rises and develops into diabetes. Among the developed countries, diabetes mellitus is a common  
5 problem and is associated with a variety of abnormalities including obesity, hypertension, hyperlipidemia (J. Clin. Invest., (1985) 75 : 809 - 817; N. Engl. J. Med. (1987) 317 : 350 - 357 ; J. Clin. Endocrinol. Metab., (1988) 66 : 580 - 583; J. Clin. Invest., (1975) 68 : 957 - 969) and other renal complications (See Patent Application No. WO 95/21608). It is now increasingly being recognized that insulin resistance and  
10 relative hyperinsulinemia have a contributory role in obesity, hypertension, atherosclerosis and type 2 diabetes mellitus. The association of insulin resistance with obesity, hypertension and angina has been described as a syndrome having insulin resistance as the central pathogenic link-Syndrome-X.

15       Hyperlipidemia is the primary cause for cardiovascular (CVD) and other peripheral vascular diseases. High risk of CVD is related to the higher LDL (Low Density Lipoprotein) and VLDL (Very Low Density Lipoprotein) seen in hyperlipidemia. Patients having glucose intolerance / insulin resistance in addition to hyperlipidemia have higher risk of CVD. Numerous studies in the past have shown that  
20 lowering of plasma triglycerides and total cholesterol, in particular LDL and VLDL and increasing HDL cholesterol help in preventing cardiovascular diseases.

Peroxisome proliferator activated receptors (PPAR) are members of the nuclear receptor super family. The gamma ( $\gamma$ ) isoform of PPAR (PPAR $\gamma$ ) has been implicated in  
25 regulating differentiation of adipocytes (Endocrinology, (1994) 135: 798-800) and energy homeostasis (Cell, (1995) 83: 803-812), whereas the alpha ( $\alpha$ ) isoform of PPAR (PPAR $\alpha$ ) mediates fatty acid oxidation (Trend. Endocrin. Metab., (1993) 4 : 291-296) thereby resulting in reduction of circulating free fatty acid in plasma (Current Biol. (1995) 5: 618 -621). PPAR $\alpha$  agonists have been found useful for the treatment of  
30 obesity (WO 97/36579). It has been recently disclosed that the hypolipidemic effect is enhanced when a molecule has both PPAR $\alpha$  and PPAR $\gamma$  agonism activity and suggested

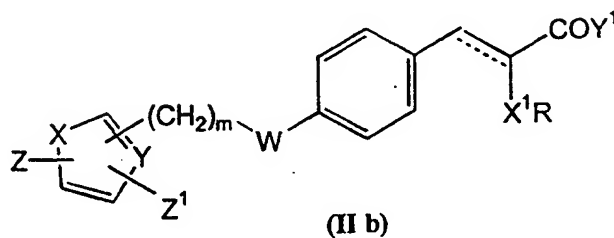
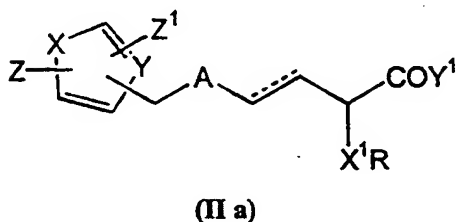
to be useful for the treatment of syndrome X (WO 97/25042). Synergism between the insulin sensitizer (PPAR $\gamma$  agonist) and HMG CoA reductase inhibitor has been observed which may be useful for the treatment of atherosclerosis and xanthoma. (EP 0 753 298).

5 It is known that PPAR $\gamma$  plays an important role in adipocyte differentiation (Cell, (1996) 87, 377-389). Ligand activation of PPAR is sufficient to cause complete terminal differentiation (Cell, (1994) 79, 1147-1156) including cell cycle withdrawal. PPAR $\gamma$  is consistently expressed in certain cells and activation of this nuclear receptor with PPAR $\gamma$  agonists would stimulate the terminal differentiation of adipocyte  
10 precursors and cause morphological and molecular changes characteristics of a more differentiated, less malignant state (Molecular Cell, (1998), 465-470; Carcinogenesis, (1998), 1949-53 ; Proc. Natl. Acad. Sci., (1997) 94, 237-241) and inhibition of expression of prostate cancer tissue (Cancer Research (1998), 58 ; 3344-3352). This would be useful in the treatment of certain types of cancer, which express PPAR $\gamma$  and  
15 could lead to a quite nontoxic chemotherapy.

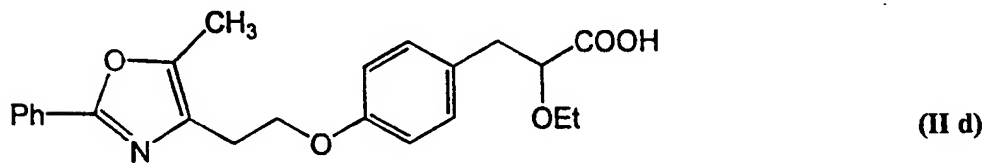
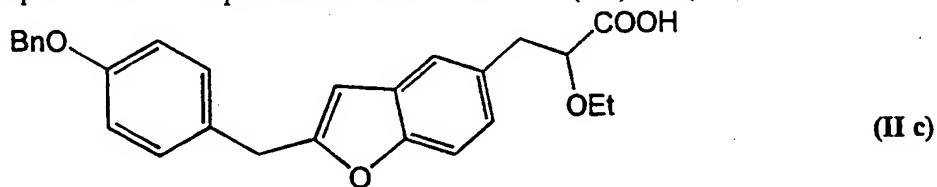
Leptin resistance is a condition wherein the target cells are unable to respond to leptin signal. This may give rise to obesity due to excess food intake and reduced energy expenditure and cause impaired glucose tolerance, type 2 diabetes, cardiovascular  
20 diseases and such other interrelated complications. Kallen *et al* (Proc. Natl. Acad. Sci., (1996) 93, 5793-5796) have reported that insulin sensitizers which perhaps due to their PPAR agonist expression and lower plasma leptin concentrations. However, it has been recently disclosed that compounds having insulin sensitizing property also possess leptin sensitization activity. They lower the circulating plasma leptin concentrations by  
25 improving the target cell response to leptin (WO 98/02159).

A few  $\beta$ -aryl- $\alpha$ -hydroxy propionic acids, their derivatives and their analogs have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia. Some of such compounds described in the prior art are outlined  
30 below :

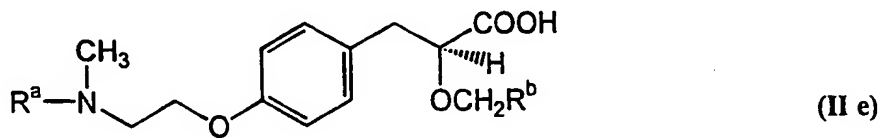
i) U.S. Pat. 5,306,726; WO 91/19702 disclose several 3-aryl-2-hydroxypropionic acid derivatives of general formula (IIa) and (IIb) as hypolipidemic and hypoglycemic agents.



Examples of these compounds are shown in formula (II c) and (II d)

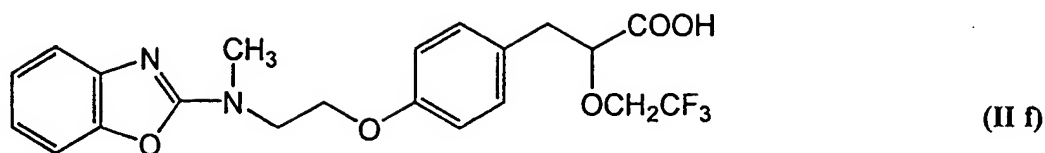


ii) International Patent Applications, WO 95/03038 and WO 96/04260 disclose compounds of formula (II e)

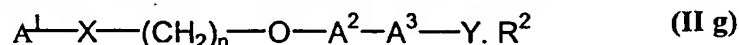


wherein R<sup>a</sup> represents 2-benzoxazolyl or 2-pyridyl and R<sup>b</sup> represent CF<sub>3</sub>, CH<sub>2</sub>OCH<sub>3</sub> or CH<sub>3</sub>. A typical example is (S)-3-[4-[2-[N-(2-benzoxazolyl)]-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid (II f).

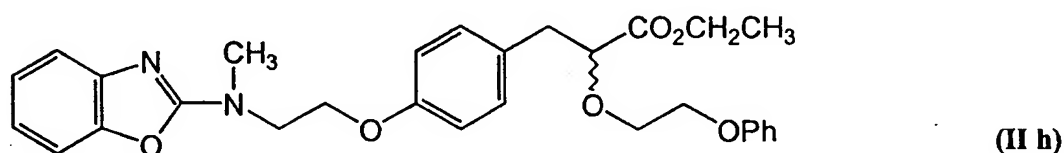
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iii) International Patent Application Nos. WO 94/13650, WO 94/01420 and WO 95/17394 disclose the compounds of general formula (II g)



- 5 wherein  $A^1$  represent aromatic heterocycle,  $A^2$  represents substituted benzene ring and  $A^3$  represents moiety of formula  $(CH_2)_m-CH-(OR^1)$ , wherein  $R^1$  represents alkyl groups,  $m$  is an integer of 1 to 5;  $X$  represents substituted or unsubstituted N;  $Y$  represents  $C=O$  or  $C=S$ .  $R^2$  represents  $OR^3$  where  $R^3$  may be alkyl, aralkyl or aryl group and  $n$  is integer in the range of 2-6. An example of these compounds is shown in formula
- 10 (II h)



### Summary of the Invention

- 15 With an objective to develop novel compounds for lowering cholesterol and reducing body weight with beneficial effects in the treatment and / or prophylaxis of diseases related to increased levels of lipids, atherosclerosis, coronary artery diseases, Syndrome-X, impaired glucose tolerance, insulin resistance, insulin resistance leading to type 2 diabetes and diabetes complications thereof, for the treatment of diseases wherein
- 20 insulin resistance is the pathophysiological mechanism, for the treatment and/or prophylaxis of leptin resistance and complications thereof, hypertension, atherosclerosis and coronary artery diseases with better efficacy, potency and lower toxicity, we focussed our research to develop new compounds effective in the treatment of above

mentioned diseases. Effort in this direction has led to compounds having general formula (I).

The main objective of the present invention is therefore, to provide novel  $\beta$ -aryl- $\alpha$ -oxysubstituted alkylcarboxylic acids and their derivatives, their analogs, their  
5 tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them, or their mixtures.

Another objective of the present invention is to provide novel  $\beta$ -aryl- $\alpha$ -oxysubstituted alkylcarboxylic acids and their derivatives, their analogs, their tautomeric  
10 forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures which may have agonist activity against PPAR $\alpha$  and / or PPAR $\gamma$ , and may inhibit HMG CoA reductase, in addition to having agonist activity against PPAR $\alpha$  and / or PPAR $\gamma$ .

15 Another objective of the present invention is to provide novel  $\beta$ -aryl- $\alpha$ -oxysubstituted alkylcarboxylic acids and their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures having enhanced activities, without toxic effect or with reduced  
20 toxic effect.

Yet another objective of the present invention is to produce a process for the preparation of novel  $\beta$ -aryl- $\alpha$ -oxysubstituted alkylcarboxylic acids and their derivatives of the formula (I) as defined above, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts and their  
25 pharmaceutically acceptable solvates.

Still another objective of the present invention is to provide pharmaceutical compositions containing compounds of the general formula (I), their analogs, their

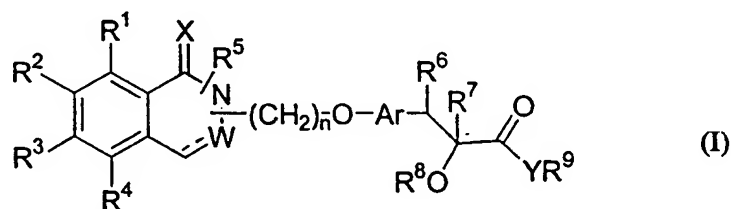
derivatives, their tautomers, their stereoisomers, their polymorphs, their salts, solvates or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

Another objective of the present invention is to provide novel intermediates, a process for the preparation of the intermediates and a process for preparing novel  $\beta$ -aryl- $\alpha$ -oxysubstituted alkylcarboxylic acids and their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates using these intermediates.

10

### Detailed Description of the Invention

$\alpha$ -Oxysubstituted propionic acids, their derivatives and their analogs of the present invention have the general formula (I)



wherein  $X$  represents  $O$  or  $S$ ; the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  may be the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of  $R^1$  to  $R^4$  together with the adjacent carbon atoms to which they are attached may also form a 5-6 membered cyclic structure containing carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains an oxo group; "----"

represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that when W represents nitrogen atom, "----" represents a bond or no bond and when W represents an oxygen atom "----" represents no bond; R<sup>5</sup> when present on carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or  
5 unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl,  
10 thioalkyl, alkylthio, aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; R<sup>5</sup> when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy,  
15 heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R<sup>6</sup>  
20 represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group R<sup>7</sup>; R<sup>7</sup> represents hydrogen, hydroxy, alkoxy, halogen, acyl, lower alkyl group or unsubstituted or substituted aralkyl or R<sup>7</sup> forms a bond together with R<sup>6</sup>; R<sup>8</sup> represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl,  
25 acyl, heterocyclyl, heteroaryl or heteroaralkyl group; R<sup>9</sup> represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; Y represents oxygen or NR<sup>10</sup>, where R<sup>10</sup> represents hydrogen, alkyl, aryl, hydroxyalkyl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; or R<sup>9</sup> and R<sup>10</sup> together may form a 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen and the linker group represented



by  $-(CH_2)_n-O-$  is attached either through nitrogen atom or through carbon atom, where  $n$  is an integer ranging from 1-4.

Suitable groups represented by  $R^1 - R^4$  and the group  $R^5$  when attached to carbon atom may be selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, or iodine; hydroxy, cyano, nitro, formyl; substituted or unsubstituted ( $C_1$ - $C_{12}$ )alkyl group, especially, linear or branched ( $C_1$ - $C_6$ )alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl and the like; cyclo( $C_3$ - $C_6$ )alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; cyclo( $C_3$ - $C_6$ )alkoxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl, naphthyl and the like, the aryl group may be substituted; aralkyl such as benzyl, phenethyl,  $C_6H_5CH_2CH_2CH_2$ , naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as  $CH_3C_6H_4CH_2$ ,  $Hal-C_6H_4CH_2$ ,  $CH_3OC_6H_4CH_2$ ,  $CH_3OC_6H_4CH_2CH_2$  and the like; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuryl and the like, the heteroaryl group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; aralkoxy group such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; aralkylamino group such as  $C_6H_5CH_2NH$ ,  $C_6H_5CH_2CH_2NH$ ,  $C_6H_5CH_2NCH_3$  and the like, which may be substituted; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl and the like, the alkoxycarbonyl group may be substituted; aryloxy carbonyl group such as phenoxycarbonyl, naphthyloxy carbonyl and the like, the aryloxy carbonyl group may be substituted; aralkoxycarbonyl group such as benzyloxy carbonyl, phenethyloxy carbonyl, naphthylmethoxy carbonyl and the like, which may be substituted; monoalkylamino group such as  $NHCH_3$ ,  $NHC_2H_5$ ,  $NHC_3H_7$ ,  $NHC_6H_{13}$  and the like, which may be substituted; dialkylamino group such as  $N(CH_3)_2$ ,  $NCH_3(C_2H_5)$ , and the like, which may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, the alkoxyalkyl

group may be substituted; aryloxyalkyl group such as  $C_6H_5OCH_2$ ,  $C_6H_5OCH_2CH_2$ , naphthyloxymethyl and the like, which may be substituted; aralkoxyalkyl group such as  $C_6H_5CH_2OCH_2$ ,  $C_6H_5CH_2OCH_2CH_2$  and the like, which may be substituted; heteroaryloxy and heteroaralkoxy, wherein heteroaryl or heteroaralkyl moieties are as defined earlier and may be substituted; aryloxy group such as phenoxy, naphthyloxy and the like, the aryloxy group may be substituted; arylamino group such as  $HNC_6H_5$ ,  $NCH_3(C_6H_5)$ ,  $NHC_6H_4CH_3$ ,  $NHC_6H_4-Hal$  and the like, the arylamino group may be substituted; amino group which may be substituted; amino( $C_1-C_6$ )alkyl, which may be substituted; hydroxy( $C_1-C_6$ )alkyl, which may be substituted; ( $C_1-C_6$ )alkoxy such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like, the alkoxy group may be substituted; thio( $C_1-C_6$ )alkyl which may be substituted; ( $C_1-C_6$ )alkylthio which may be substituted; acyl group such as acetyl, propionyl, benzoyl and the like, the acyl group may be substituted; acylamino groups such as  $NHCOCH_3$ ,  $NHCOC_2H_5$ ,  $NHCOC_3H_7$ ,  $NHCOC_6H_5$  and the like, the acylamino group may be substituted; aralkoxycarbonylamino group such as  $NHCOOCH_2C_6H_5$ ,  $NHCOOCH_2CH_2C_6H_5$ ,  $N(CH_3)COOCH_2C_6H_5$ ,  $N(C_2H_5)COOCH_2C_6H_5$ ,  $NHCOOCH_2C_6H_4CH_3$ ,  $NHCOOCH_2C_6H_4OCH_3$  and the like, the aralkoxycarbonylamino group may be substituted; aryloxycarbonylamino group such as  $NHCOOC_6H_5$ ,  $NCH_3COOC_6H_5$ ,  $NC_2H_5COOC_6H_5$ ,  $NHCOOC_6H_4CH_3$ ,  $NHCOOC_6H_4OCH_3$  and the like, the aryloxycarbonylamino group may be substituted; alkoxycarbonylamino group such as  $NHCOOC_2H_5$ ,  $NHCOOCH_3$  and the like, the alkoxycarbonylamino group may be substituted; carboxylic acid or its derivatives such as amides, like  $CONH_2$ ,  $CONHMe$ ,  $CONMe_2$ ,  $CONH_2$ ,  $CONH_2$ ,  $CONH_2$ ,  $CONH_2$  and the like, the carboxylic acid derivatives may be substituted; acyloxy group such as  $OOCMe$ ,  $OOC_2H_5$ ,  $OOCPh$  and the like, the acyloxy group may be substituted; sulfonic acid or its derivatives such as  $SO_2NH_2$ ,  $SO_2NHMe$ ,  $SO_2NMe_2$ ,  $SO_2NHCF_3$  and the like, the sulfonic acid derivatives may be substituted.

When the groups represented by  $R^1$ -  $R^4$  and the group  $R^5$  when attached to carbon atom are substituted, the substituents may be selected from halogen, hydroxy, nitro or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aralkoxy, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl,

aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives. These groups are as defined above.

It is preferred that the substituents on  $R^1 - R^4$  and  $R^5$  when attached to carbon atom represent halogen atom such as fluorine, chlorine, bromine; alkyl group such as methyl, ethyl, isopropyl, n-propyl, n-butyl; ( $C_3-C_6$ )cycloalkyl group such as cyclopropyl; aryl group such as phenyl; aralkyl group such as benzyl; ( $C_1-C_3$ )alkoxy, benzyloxy, hydroxy group, acyl or acyloxy groups.

Suitable groups represented by any two of  $R^1$  to  $R^4$  which form the cyclic structure together with the adjacent carbon atoms to which they are attached may be selected from  $-OCH_2O-$ ,  $-OCH_2CH_2O-$ ,  $-OCOO-$ ,  $-CH_2COO-$ ,  $-OCH_2CH_2NH-$ ,  $-OCH_2NH-$ ,  $-OCH_2CH_2S-$ ,  $-NHCH_2CH_2O-$ ,  $-NHCOCH_2O-$ ,  $-CH_2COCH_2-$  and the like, preferably  $-OCH_2O-$  and  $-OCH_2CH_2O-$  groups.

Suitable  $R^5$  when attached to a nitrogen atom is selected from hydrogen, hydroxy, formyl; substituted or unsubstituted ( $C_1-C_{12}$ )alkyl group, especially, linear or branched ( $C_1-C_6$ )alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl, t-butyl, n-pentyl, iso-pentyl, hexyl and the like; cyclo( $C_3-C_6$ )alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; cyclo( $C_3-C_6$ )alkyloxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl such as benzyl, phenethyl,  $C_6H_5CH_2CH_2CH_2$ , naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as  $CH_3C_6H_4CH_2$ ,  $Hal-C_6H_4CH_2$ ,  $CH_3OC_6H_4CH_2$ ,  $CH_3OC_6H_4CH_2CH_2$  and the like; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuryl and the like, the heteroaryl group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; aralkoxy group such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; alkylamino group such as  $C_6H_5CH_2NH$ ,  $C_6H_5CH_2CH_2NH$ ,  $C_6H_5CH_2NCH_3$

and the like, which may be substituted; alkoxy carbonyl such as methoxy carbonyl, ethoxy carbonyl and the like, the alkoxy carbonyl group may be substituted; aryloxy carbonyl group such as phenoxy carbonyl, naphthoxy carbonyl and the like, the aryloxy carbonyl group may be substituted; aralkoxy carbonyl group such as benzyloxy carbonyl, phenethyloxy carbonyl, naphthylmethoxy carbonyl and the like, which may be substituted; monoalkylamino group such as  $\text{NHCH}_3$ ,  $\text{NHC}_2\text{H}_5$ ,  $\text{NHC}_3\text{H}_7$ ,  $\text{NHC}_6\text{H}_{13}$  and the like, the monoalkylamino group may be substituted; dialkylamino group such as  $\text{N}(\text{CH}_3)_2$ ,  $\text{NCH}_3(\text{C}_2\text{H}_5)$ , and the like, the dialkylamino group may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, the alkoxyalkyl group may be substituted; aryloxyalkyl group such as  $\text{C}_6\text{H}_5\text{OCH}_2$ ,  $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2$ , naphthoxyethyl and the like, which may be substituted; aralkoxyalkyl group such as  $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$ ,  $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2$  and the like, which may be substituted; heteroaryloxy and heteroaralkoxy, wherein heteroaryl moiety is as defined earlier and may be substituted; aryloxy group such as phenoxy, naphthoxy and the like, the aryloxy group may be substituted; arylamino group such as  $\text{HNC}_6\text{H}_5$ ,  $\text{NCH}_3(\text{C}_6\text{H}_5)$ ,  $\text{NHC}_6\text{H}_4\text{CH}_3$ ,  $\text{NHC}_6\text{H}_4\text{-Hal}$  and the like, the arylamino group may be substituted; amino group, which may be substituted; amino( $\text{C}_1\text{-C}_6$ )alkyl which may be substituted; hydroxy( $\text{C}_1\text{-C}_6$ )alkyl which may be substituted; ( $\text{C}_1\text{-C}_6$ )alkoxy such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like, which may be substituted; thio( $\text{C}_1\text{-C}_6$ )alkyl, which may be substituted; ( $\text{C}_1\text{-C}_6$ )alkylthio, which may be substituted; acyl group such as acetyl, propionyl, benzoyl and the like, the acyl group may be substituted; acylamino groups such as  $\text{NHCOCH}_3$ ,  $\text{NHCOC}_2\text{H}_5$ ,  $\text{NHCOC}_3\text{H}_7$ ,  $\text{NHCOC}_6\text{H}_5$  and the like the acylamino group may be substituted; carboxylic acid derivatives such as amides, like  $\text{CONH}_2$ ,  $\text{CONHMe}$ ,  $\text{CONMe}_2$ ,  $\text{CONHEt}$ ,  $\text{CONEt}_2$ ,  $\text{CONHPh}$  and the like, the carboxylic acid derivatives may be substituted; acyloxy group such as  $\text{OOCMe}$ ,  $\text{OOCeEt}$ ,  $\text{OOCPh}$  and the like which may be substituted; sulfonic acid derivatives such as  $\text{SO}_2\text{NH}_2$ ,  $\text{SO}_2\text{NHMe}$ ,  $\text{SO}_2\text{NMe}_2$ ,  $\text{SO}_2\text{NHCF}_3$  and the like, the sulfonic acid derivatives may be substituted.

When the groups represented by  $\text{R}^5$  attached to nitrogen are substituted, preferred substituents may be selected from halogen such as fluorine, chlorine; hydroxy, acyl, acyloxy and amino groups.

When  $\text{R}^5$  is attached to nitrogen atom,  $\text{R}^1\text{-R}^4$  are the same as defined earlier.

The group represented by Ar includes substituted or unsubstituted groups selected from divalent phenylene, naphthylene, pyridyl, quinolinyl, benzofuryl, benzopyranyl, benzoxazolyl, benzothiazolyl, indolyl, indolinyl, azaindolyl, azaindolyl, indenyl, dihydrobenzofuryl, dihydrobenzopyranyl, pyrazolyl and the like. The substituents on the group represented by Ar include linear or branched optionally halogenated (C<sub>1</sub>-C<sub>6</sub>)alkyl, optionally halogenated (C<sub>1</sub>-C<sub>3</sub>)alkoxy, halogen, acyl, amino, acylamino, thio, carboxylic and sulfonic acids and their derivatives. The substituents are defined as they are for R<sup>1</sup>-R<sup>4</sup>.

It is more preferred that Ar represents a substituted or unsubstituted divalent, phenylene, naphthylene, benzofuryl, indolyl, indolinyl, quinolinyl, azaindolyl, azaindolyl, benzothiazolyl or benzoxazolyl groups.

It is still more preferred that Ar represents a divalent phenylene or naphthylene, which may be unsubstituted or substituted by methyl, halomethyl, methoxy or halomethoxy groups.

Suitable R<sup>6</sup> includes hydrogen, lower alkyl groups such as methyl, ethyl or propyl; hydroxy, (C<sub>1</sub>-C<sub>3</sub>)alkoxy; halogen atom such as fluorine, chlorine, bromine or iodine; aralkyl such as benzyl, phenethyl, which may be unsubstituted or substituted with halogen, hydroxy, (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, benzyloxy, acetyl, acetyloxy groups or R<sup>6</sup> together with R<sup>7</sup> represent a bond.

Suitable R<sup>7</sup> may be hydrogen, lower alkyl groups such as methyl, ethyl or propyl; hydroxy, (C<sub>1</sub>-C<sub>3</sub>)alkoxy; halogen atom such as fluorine, chlorine, bromine, iodine; acyl group such as linear or branched (C<sub>2</sub>-C<sub>10</sub>)acyl group such as acetyl, propanoyl, butanoyl, pentanoyl, benzoyl and the like; aralkyl such as benzyl, phenethyl, which may be unsubstituted or substituted with halogen, hydroxy, (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, benzyloxy, acetyl or acetyloxy groups or together with R<sup>6</sup> forms a bond.

It is preferred that R<sup>6</sup> and R<sup>7</sup> represent hydrogen atom or R<sup>6</sup> and R<sup>7</sup> together represent a bond.

Suitable groups represented by R<sup>8</sup> may be selected from hydrogen, linear or branched (C<sub>1</sub>-C<sub>16</sub>)alkyl, preferably (C<sub>1</sub>-C<sub>12</sub>)alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, pentyl, hexyl, octyl and the like, the alkyl group group may be substituted; (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, the cycloalkyl group may be substituted; aryl

group such as phenyl, naphthyl and the like, the aryl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl and the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; aralkyl group  
5 wherein the aryl group is as defined earlier and the alkyl moiety may contain (C<sub>1</sub>-C<sub>6</sub>) atoms, such as benzyl and phenethyl and the like, the aralkyl group may be substituted; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl and the like, the heterocyclyl group may be substituted; (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxypropyl and the like, the  
10 alkoxyalkyl group may be substituted; linear or branched (C<sub>2</sub>-C<sub>16</sub>)acyl group such as acetyl, propanoyl, isopropanoyl, butanoyl, benzoyl, octanoyl, decanoyl and the like, the (C<sub>2</sub>-C<sub>16</sub>)acyl group may be substituted; (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, and the like, the alkoxycarbonyl group may be substituted; aryloxy carbonyl such as phenoxycarbonyl, naphthyloxy carbonyl and the  
15 like, the aryl group may be substituted; (C<sub>1</sub>-C<sub>6</sub>)alkylaminocarbonyl, the alkyl group may be substituted or arylaminocarbonyl such as PhNHCO, naphthylaminocarbonyl and the like, the aryl moiety may be substituted. The substituents may be selected from halogen, hydroxy, formyl or nitro or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aralkoxyalkyl, heterocyclyl, heteroaryl,  
20 heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives. These groups are as defined above.

Suitable groups represented by R<sup>9</sup> may be selected from hydrogen, linear or  
25 branched (C<sub>1</sub>-C<sub>16</sub>)alkyl, preferably (C<sub>1</sub>-C<sub>12</sub>)alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, pentyl, hexyl, octyl and the like, the (C<sub>1</sub>-C<sub>16</sub>)alkyl group may be substituted; (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl such as cyclopropyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; aryl group such as phenyl, naphthyl, the aryl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl and  
30 the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; aralkyl group such as benzyl, phenethyl and the like, the

aralkyl group may be substituted; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl and the like, the heterocyclyl group may be substituted. The substituents on  $R^9$  may be selected from the same group as  $R^1$ - $R^4$ .

Suitable groups represented by  $R^{10}$  may be selected from hydrogen, linear or  
5 branched ( $C_1$ - $C_{16}$ )alkyl, preferably ( $C_1$ - $C_{12}$ )alkyl; hydroxy( $C_1$ - $C_6$ )alkyl; aryl group such as phenyl, naphthyl and the like; aralkyl group such as benzyl, phenethyl and the like; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl, and the like; heteroaryl group such as pyridyl, thienyl, furyl and the like; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like.

10 Suitable ring structures formed by  $R^9$  and  $R^{10}$  together may be selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl and the like.

Suitable n is an integer ranging from 1 to 4, preferably n represents an integer 1 or 2.

Pharmaceutically acceptable salts forming part of this invention include salts of  
15 the carboxylic acid moiety such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as diethanolamine, choline and the like, salts of natural aminoacids such as lysine, arginine, glycine, guanidine and the like, salts of unnatural aminoacids such as D-isomers or substituted aminoacids, ammonium or substituted ammonium salts and aluminum salts. Salts may  
20 include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of  
25 crystallization such as alcohols.

Particularly useful compounds according to the present invention include :

- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;  
30 (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
propanoate;

- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- 5 (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- (±) Ethyl 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
10 propanoate ;
- (+) Ethyl 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- (-) Ethyl 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- 15 (±) Ethyl 2-methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- (+) Ethyl 2-methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- (-) Ethyl 2-methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
20 propanoate ;
- (±) Ethyl-2-propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- (+) Ethyl-2-propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- 25 (-) Ethyl-2-propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]  
propanoate ;
- (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]  
30 propanoate ;



- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 5 (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 10 (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 15 (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 20 (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 25 (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 30

- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoate ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 5 (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 10 (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 15 (±) 2-Hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (+) 2-Hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (-) 2-Hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 20 (±) 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (+) 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 25 (-) 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (±) 2-Propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (+) 2-Propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 30

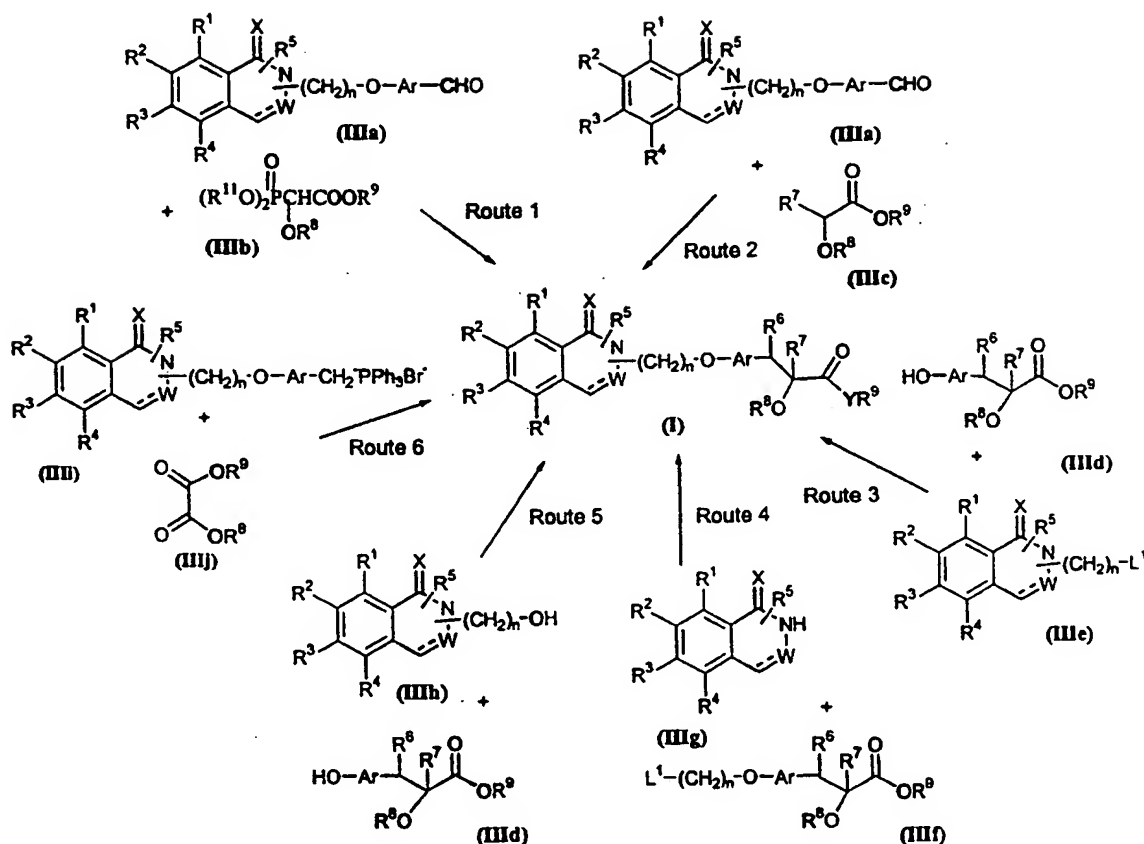
- (-) 2-Propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- (±) Butyl 2-butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 5 (+) Butyl 2-butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (-) Butyl 2-butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (±) 2-Butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- 10 (+) 2-Butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- (-) 2-Butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- 15 (±) Benzyl 2-benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (+) Benzyl 2-benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (-) Benzyl 2-benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 20 (±) 2-Benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- (+) 2-Benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- 25 (-) 2-Benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- 30 (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]

- propanoic acid and its salts ;  
(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyloxy)]phenyl]  
5 propanoic acid and its salts ;  
(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
10 (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyloxy)]phenyl]  
15 propanoic acid and its salts ;  
(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
20 (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyloxy)]phenyl]  
25 propanoic acid and its salts ;  
(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;  
30 (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyloxy)]phenyl]  
propanoic acid and its salts ;

- [2R, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- [2S, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- 5 [(2R), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-isopropylethyl)propanamide ;
- [(2S), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-isopropylethyl)propanamide ;
- [2R, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]
- 10 phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- [2S, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- [2R, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- 15 [2S, 2N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid lysine salt ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid
- 20 arginine salt and
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid magnesium salt.

According to a feature of the present invention, the compound of general formula

25 (I) where  $R^6$  and  $R^7$  together represent a bond, Y represents oxygen atom,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , X, W,  $R^8$ ,  $R^9$ , n and Ar are as defined earlier, may be prepared by any of the following routes shown in Scheme I.



Scheme - I

**Route 1 :** The reaction of a compound of the general formula (IIIa) where all symbols are as defined earlier with a compound of formula (IIIb), where R<sup>11</sup> may be a lower alkyl group and R<sup>8</sup> and R<sup>9</sup> are as defined earlier excluding hydrogen, to yield a compound of general formula (I) defined above, may be carried out in the presence of a base such as alkali metal hydrides like NaH or KH or organolithiums like CH<sub>3</sub>Li, BuLi and the like or alkoxides such as NaOMe, NaOEt, K<sup>+</sup>BuO<sup>-</sup> or mixtures thereof. The reaction may be carried out in presence of solvents such as THF, dioxane, DMF, DMSO, DME and the like or mixtures thereof. HMPA may be used as cosolvent. The reaction temperature may range from -78 °C to 50 °C, preferably at a temperature in the range of -10 °C to 30 °C. The reaction is more effective under anhydrous conditions. The compound of general formula (IIIb) may be prepared according to the procedure described in the literature (Annalen. Chemie, (1996) 53, 699)

Alternatively, the compound of formula (I) may be prepared by reacting the compound of formula (IIIa) where all symbols are as defined earlier with Wittig reagents such as  $\text{HalPH}_3\text{P}^+\text{CH}-(\text{OR}^8)\text{CO}_2\text{R}^9$  under similar reaction conditions as described above.

5

Route 2 : The reaction of a compound of the general formula (IIIa) where all symbols are as defined earlier with a compound of formula (IIIc) where  $\text{R}^7$  represents a hydrogen atom and  $\text{R}^8$  and  $\text{R}^9$  are as defined earlier may be carried out in the presence of a base. The nature of the base is not critical. Any base normally employed for aldol  
10 condensation reaction may be employed; bases like metal hydride such as NaH or KH, metal alkoxides such as NaOMe,  $\text{K}^+\text{BuO}^-$  or NaOEt, metal amides such as  $\text{LiNH}_2$  or  $\text{LiN}(\text{iPr})_2$  may be used. Aprotic solvent such as THF, ether or dioxane may be used. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as  $\text{N}_2$ , Ar, or He and the reaction is more effective under anhydrous  
15 conditions. Temperature in the range of  $-80\text{ }^\circ\text{C}$  to  $35\text{ }^\circ\text{C}$  may be used. The  $\beta$ -hydroxy product initially produced may be dehydrated under conventional dehydration conditions such as treating with pTSA in solvents such as benzene or toluene. The nature of solvent and dehydrating agent is not critical. Temperature in the range of  $20\text{ }^\circ\text{C}$  to reflux temperature of the solvent used may be employed, preferably at reflux temperature of  
20 the solvent by continuous removal of water using a Dean Stark water separator.

Route 3 : The reaction of compound of formula (IIIe) where all symbols are as defined earlier and  $\text{L}^1$  represents a leaving group such as as halogen atom, p-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate and the like, preferably a halogen atom  
25 with a compound of formula (IIId) where  $\text{R}^6$  and  $\text{R}^7$  together represent a bond and  $\text{R}^8$ ,  $\text{R}^9$  and Ar are as defined earlier to produce a compound of the formula (I) defined above may be carried out in the presence of aprotic solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as  $\text{N}_2$ , Ar, or He. The reaction may  
30 be effected in the presence of a base such as  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$  or NaH or mixtures thereof. Acetone may be used as solvent when  $\text{Na}_2\text{CO}_3$  or  $\text{K}_2\text{CO}_3$  is used as a base. The

reaction temperature may range from 0 °C - 120 °C, preferably at a temperature in the range of 30 °C - 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 12 hours. The compound of formula (IIIId) can be prepared according to known procedure by a Wittig Horner reaction between the protected  
5 hydroxy aryl aldehyde such as benzyloxy aryl aldehyde and compound of formula (IIIb), followed by the reduction of double bond and deprotection.

Route 4 : The reaction of a compound of general formula (IIIg) where all symbols are as defined earlier with a compound of general formula (IIIf) where R<sup>6</sup>, R<sup>7</sup> together  
10 represent a bond and all other symbols are as defined earlier and L<sup>1</sup> is a leaving group such as halogen atom, p-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate and the like, preferably a halogen atom to produce a compound of general formula (I) defined above where the -(CH<sub>2</sub>)<sub>n</sub>-O- is attached through nitrogen atom may be carried out in the presence of solvents such as DMSO, DMF, DME, THF, dioxane, ether and  
15 the like or a combination thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N<sub>2</sub>, Ar or He. The reaction may be effected in the presence of a base such as alkalis like sodium hydroxide or potassium hydroxide; alkali metal carbonates like sodium carbonate or potassium carbonate; alkali metal hydrides such as sodium hydride or potassium hydride;  
20 organometallic bases like n-butyl lithium; alkali metal amides like sodamide or mixtures thereof. The amount of base may range from 1 to 5 equivalents, based on the amount of the compound of formula (IIIg), preferably the amount of base ranges from 1 to 3 equivalents. Phase transfer catalysts such as tetraalkylammonium halide or hydroxide may be added. Additives like alkali metal halides such as LiBr may be used. The  
25 reaction may be carried out at a temperature in the range of 0 °C to 150 °C, preferably at a temperature in the range of 15 °C to 100 °C. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.25 to 12 hours.

Route 5 : The reaction of compound of general formula (IIIh) where all symbols are as  
30 defined earlier with a compound of general formula (IIIId) where R<sup>6</sup> and R<sup>7</sup> together represent a bond and R<sup>8</sup>, R<sup>9</sup> and Ar are as defined earlier may be carried out using

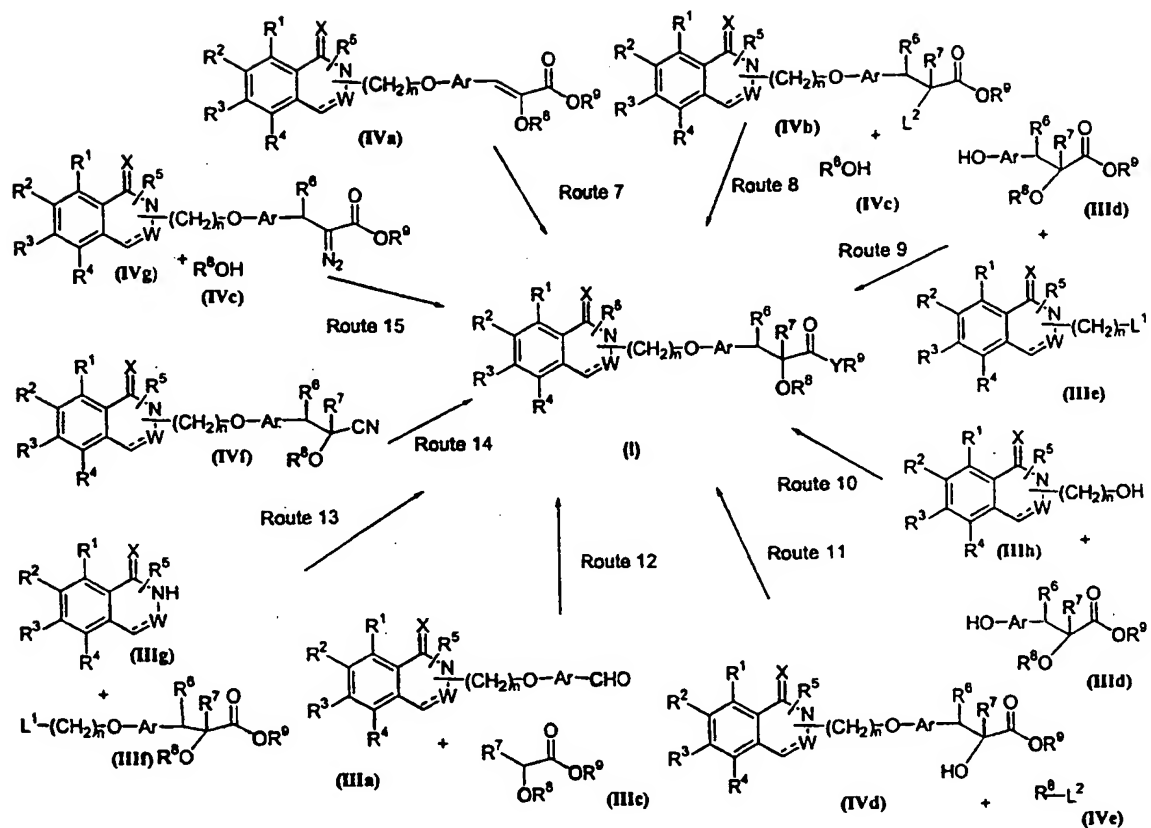


suitable coupling agents such as dicyclohexyl urea, triarylphosphine/dialkylazadicarboxylate such as  $\text{PPh}_3$  / DEAD and the like. The reaction may be carried out in the presence of solvents such as THF, DME,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ , toluene, acetonitrile, carbontetrachloride and the like. The inert atmosphere may  
5 be maintained by using inert gases such as  $\text{N}_2$ , Ar or He. The reaction may be effected in the presence of DMAP, HOBt and they may be used in the range of 0.05 to 2 equivalents, preferably 0.25 to 1 equivalents. The reaction temperature may be in the range of  $0^\circ\text{C}$  to  $100^\circ\text{C}$ , preferably at a temperature in the range of  $20^\circ\text{C}$  to  $80^\circ\text{C}$ . The duration of the reaction may range from 0.5 to 24 hours, preferably from 6 to 12 hours.

10 Route 6: The reaction of a compound of formula (IIIi) where all symbols are as defined earlier with a compound of formula (IIIj) where  $\text{R}^8 = \text{R}^9$  and are as defined earlier excluding hydrogen, to produce a compound of the formula (I) where  $\text{R}^6$  and  $\text{R}^7$  together represent a bond may be carried out neat in the presence of a base such as alkali metal hydrides like NaH or KH or organolithiums like  $\text{CH}_3\text{Li}$ , BuLi and the like or alkoxides  
15 such as NaOMe, NaOEt,  $\text{K}^+\text{BuO}^-$  and the like or mixtures thereof. The reaction may be carried out in the presence of aprotic solvents such as THF, dioxane, DMF, DMSO, DME and the like or mixtures thereof. HMPA may be used as cosolvent. The reaction temperature may range from  $-78^\circ\text{C}$  to  $100^\circ\text{C}$ , preferably at a temperature in the range of  $-10^\circ\text{C}$  to  $50^\circ\text{C}$ .

20

According to another embodiment of the present invention, the compound of the general formula (I) where  $\text{R}^6$  represents hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or substituted aralkyl group;  $\text{R}^7$  represents hydroxy, alkoxy, halogen, acyl, lower alkyl or unsubstituted or substituted aralkyl group;  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ , X, W,  $\text{R}^8$ ,  
25  $\text{R}^9$ , n, and Ar as defined earlier and Y represents oxygen atom can be prepared by one or more of the processes shown in Scheme - II:



## Scheme - II

- Route 7 :** The reduction of compound of the formula (IVa) which represents a compound of formula (I) where  $R^6$  and  $R^7$  together represent a bond and Y represents an oxygen atom and all other symbols are as defined earlier, may be obtained as described earlier in Scheme-I, to yield a compound of the general formula (I) where  $R^6$  and  $R^7$  each represent hydrogen atom and all other symbols are as defined earlier, may be carried out in the presence of gaseous hydrogen and a catalyst such as Pd/C, Rh/C, Pt/C, and the like. Mixtures of catalysts may be used. The reaction may also be conducted in the presence of solvents such as dioxane, acetic acid, ethyl acetate or alcohol such as methanol, ethanol and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5 - 10 % Pd/C and the amount of catalyst used may range from 5 - 100 % w/w. The reaction may also be carried out by employing metal solvent reduction such as magnesium in alcohol or sodium amalgam in alcohol, preferably methanol. The hydrogenation may be carried out in the presence of

metal catalysts containing chiral ligands to obtain a compound of formula (I) in optically active form. The metal catalyst may contain Rhodium, Ruthenium, Indium and the like. The chiral ligands may preferably be chiral phosphines such as (2S,3S)-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(2-methoxyphenylphosphino)ethane, (-)-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane and the like. Any suitable chiral catalyst may be employed which would give required optical purity of the product (I) (Ref : Principles of Asymmetric Synthesis, Tet. Org. Chem. Series Vol 14, pp311-316, Ed. Baldwin J. E.).

10 Route 8 : The reaction of compound of formula (IVb) where  $R^9$  is as defined earlier excluding hydrogen and all other symbols are as defined earlier and  $L^2$  is a leaving group such as halogen atom with an alcohol of general formula (IVc), where  $R^8$  is as defined earlier excluding hydrogen to produce a compound of the formula (I) defined earlier may be carried out in the presence of solvents such as THF, DMF, DMSO, DME  
15 and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as  $N_2$ , Ar, or He. The reaction may be effected in the presence of a base such as KOH, NaOH, NaOMe, NaOEt,  $K^+BuO^-$  or NaH or mixtures thereof. Phase transfer catalysts such as tetraalkylammonium halides or hydroxides may be employed. The reaction temperature may range from 20 °C - 120  
20 °C, preferably at a temperature in the range of 30 °C - 100 °C. The duration of the reaction may range from 1 to 12 hours, preferably from 2 to 6 hours. The compound of general formula (IVb) and its preparation has been disclosed in international application No. US98/07285.

25 Route 9 : The reaction of compound of formula (IIIe) defined earlier with a compound of formula (IIId) where all symbols are as defined earlier to produce a compound of the formula (I) where all symbols are as defined above, may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which is maintained by using inert  
30 gases such as  $N_2$ , Ar or He. The reaction may be effected in the presence of a base such as  $K_2CO_3$ ,  $Na_2CO_3$  or NaH or mixtures thereof. Acetone may be used as a solvent

when  $K_2CO_3$  or  $Na_2CO_3$  is used as a base. The reaction temperature may range from 20 °C - 120 °C, preferably at a temperature in the range of 30 °C - 80 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 12 hours. The compound of formula (IIIId) may be prepared by Wittig Horner reaction between the protected hydroxyaryl aldehyde and compound of formula (IIIf) followed by reduction of the double bond and deprotection. Alternatively, the compound of formula (IIIId) may be prepared by following a procedure disclosed in WO 94/01420.

Route 10 : The reaction of compound of general formula (IIIh) defined earlier with a compound of general formula (IIIId) where all symbols are as defined earlier to produce a compound of the formula (I) where all symbols are as defined above may be carried out using suitable coupling agents such as dicyclohexyl urea, triarylphosphine/dialkylazodicarboxylate such as  $PPh_3$  / DEAD and the like. The reaction may be carried out in the presence of solvents such as THF, DME,  $CH_2Cl_2$ ,  $CHCl_3$ , toluene, acetonitrile, carbon tetrachloride and the like. The inert atmosphere may be maintained by using inert gases such as  $N_2$ , Ar or He. The reaction may be effected in the presence of DMAP, HOBT and they may be used in the range of 0.05 to 2 equivalents, preferably 0.25 to 1 equivalents. The reaction temperature may be in the range of 0 °C to 100 °C, preferably at a temperature in the range of 20 °C to 80 °C. The duration of the reaction may range from 0.5 to 24 hours, preferably from 6 to 12 hours.

Route 11 : The reaction of compound of formula (IVd) which represents a compound of formula (I) where all symbols are as defined earlier with a compound of formula (IVe) where  $R^8$  represents unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl and  $L^2$  is a leaving group such as halogen atom, may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like. The inert atmosphere may be maintained by using inert gases such as  $N_2$ , Ar or He. The reaction may be effected in the presence of a base such as KOH, NaOH, NaOMe,  $K^+BuO^-$ , NaH and the like. Phase transfer catalyst such as tetraalkylammoniumhalides or hydroxides may be employed. The reaction

temperature may range from 20 °C to 150 °C, preferably at a temperature in the range of 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours. The compound of formula (IVd) represents compound of formula (I) where  $R^8$  represents H and Y represents oxygen atom.

5

Route 12 : The reaction of a compound of the general formula (IIIa) as defined earlier with a compound of formula (IIIc) where  $R^7$ ,  $R^8$  and  $R^9$  are as defined earlier may be carried out under conventional conditions. The base is not critical. Any base normally employed for aldol condensation reaction may be employed, metal hydride such as NaH, 10 or KH; metal alkoxides such as NaOMe,  $K^tBuO^-$  or NaOE; metal amides such as  $LiNH_2$  or  $LiN(iPr)_2$ . Aprotic solvent such as THF may be used. Inert atmosphere may be employed such as argon and the reaction is more effective under anhydrous conditions. Temperature in the range of -80 °C to 25 °C may be used. The  $\beta$ -hydroxy aldol product may be dehydroxylated using conventional methods, conveniently by ionic 15 hydrogenation technique such as by treating with a trialkyl silane in the presence of an acid such as trifluoroacetic acid. Solvent such as  $CH_2Cl_2$  may be used. Favorably, the reaction proceeds at 25 °C. Higher temperature may be employed if the reaction is slow.

Route 13 : The reaction of a compound of general formula (IIIg) where all symbols are 20 as defined earlier with a compound of general formula (IIIf) where  $L^1$  is a leaving group such as halogen atom, p-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate and the like, preferably a halogen atom, all other symbols are as defined earlier to produce a compound of general formula (I) defined above where the  $-(CH_2)_n-O-$  is attached through nitrogen atom may be carried out in the presence of solvents such as 25 DMSO, DMF, DME, THF, dioxane, ether and the like or a combination thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as  $N_2$ , Ar or He. The reaction may be effected in the presence of a base such as alkalis like sodium hydroxide or potassium hydroxide; alkali metal carbonates like sodium carbonate or potassium carbonate; alkali metal hydrides such as sodium 30 hydride or potassium hydride; organometallic bases like n-butyl lithium; alkali metal amides like sodamide or mixtures thereof. The amount of base may range from 1 to 5

equivalents, based on the amount of the compound of formula (IIIg), preferably the amount of base ranges from 1 to 3 equivalents. The reaction may be carried out at a temperature in the range of 0 °C to 150 °C, preferably at a temperature in the range of 15 °C to 100 °C. The duration of the reaction may range from 0.25 to 24 hours, preferably from 0.25 to 12 hours.

Route 14 : The conversion of compound of formula (IVf) where all symbols are as defined earlier to a compound of formula (I) may be carried out either in the presence of base or acid and the selection of base or acid is not critical. Any base normally used for hydrolysis of nitrile to acid may be employed, metal hydroxides such as NaOH or KOH in an aqueous solvent or any acid normally used for hydrolysis of nitrile to ester may be employed such as dry HCl in an excess of alcohol such as methanol, ethanol, propanol and the like. The reaction may be carried out at a temperature in the range of 0 °C to reflux temperature of the solvent used, preferably at a temperature in the range of 25 °C to reflux temperature of the solvent used. The duration of the reaction may range from 0.25 to 48 hrs.

Route 15 : The reaction of a compound of formula (IVg) where  $R^9$  is as defined earlier excluding hydrogen all symbols are as defined earlier with a compound of formula (IVc) where  $R^8$  is as defined earlier excluding hydrogen to produce a compound of formula (I) (by a rhodium carbenoid mediated insertion reaction) may be carried out in the presence of rhodium (II) salts such as rhodium (II) acetate. The reaction may be carried out in the presence of solvents such as benzene, toluene, dioxane, ether, THF and the like or a combination thereof or when practicable in the presence of  $R^8OH$  as solvent at any temperature providing a convenient rate of formation of the required product, generally at an elevated temperature, such as reflux temperature of the solvent. The inert atmosphere may be maintained by using inert gases such as  $N_2$ , Ar or He. The duration of the reaction may range from 0.5 to 24 h, preferably from 0.5 to 6 h.

The compound of formula (I) where  $R^9$  represents hydrogen atom may be prepared by hydrolysing using conventional methods, a compound of formula (I) where  $R^9$  represents all groups defined earlier except hydrogen. The hydrolysis may be carried out in the presence of a base such as  $Na_2CO_3$  and a suitable solvent such as methanol,

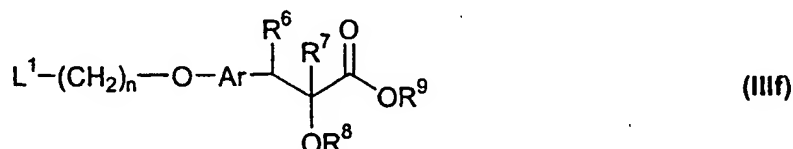
ethanol and the like or mixtures thereof. The reaction may be carried out at a temperature in the range of 20 °C - 40 °C, preferably at 25 °C - 30 °C. the reaction time may range from 2 to 12 h, preferably from 4 to 8 h.

- 5           The compound of general formula (I) where Y represents oxygen and R<sup>9</sup> represents hydrogen or lower alkyl groups as defined earlier may be converted to compound of formula (I), where Y represents NR<sup>10</sup> by reaction with appropriate amines of the formula NHR<sup>9</sup>R<sup>10</sup>, where R<sup>9</sup> and R<sup>10</sup> are as defined earlier. Alternatively, the compound of formula (I) where YR<sup>9</sup> represents OH may be converted to acid halide, preferably YR<sup>9</sup> = Cl, by reacting with appropriate reagents such as oxalyl chloride, 10 thionyl chloride and the like, followed by treatment with amines of the formula NHR<sup>9</sup>R<sup>10</sup>, where R<sup>9</sup> and R<sup>10</sup> are as defined earlier. Alternatively, mixed anhydrides may be prepared from compound of formula (I) where YR<sup>9</sup> represents OH and all other symbols are as defined earlier by treating with acid halides such as acetyl chloride, acetyl 15 bromide, pivaloyl chloride and the like. The reaction may be carried in the presence of suitable base such as pyridine, triethylamine, diisopropyl ethyl amine and the like. Solvents such as halogenated hydrocarbons like CHCl<sub>3</sub> or CH<sub>2</sub>Cl<sub>2</sub>, hydrocarbons such as benzene, toluene, xylene and the like may be used. The reaction may be carried out at a temperature in the range of -40 °C to 40 °C, preferably 0 °C to 20 °C. The acid halide or 20 mixed anhydride thus prepared may further be treated with appropriate amines of the formula NHR<sup>9</sup>R<sup>10</sup>, where R<sup>9</sup> and R<sup>10</sup> are as defined earlier.

The processes for the preparation of compounds of general formula (IIIa) have been described in international application No. US98/07285.

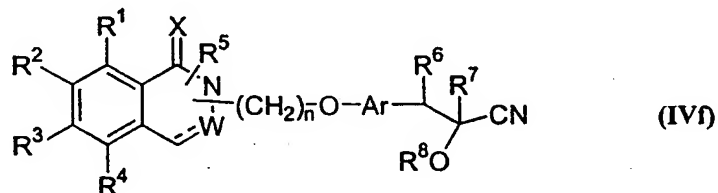
- 25           As used herein the term neat means the reaction is carried out without the use of a solvent.

The process for the preparation of intermediate of formula (IIIf)



where  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ , Ar and n are as defined earlier, and  $L^1$  is a leaving group and a process for its preparation and its use in the preparation of  $\beta$ -aryl- $\alpha$ -substituted hydroxyalkanoic acids has been provided in international application No. US98/01397.

In another embodiment of the present invention there is provided a novel  
 5 intermediate of formula (IVf)

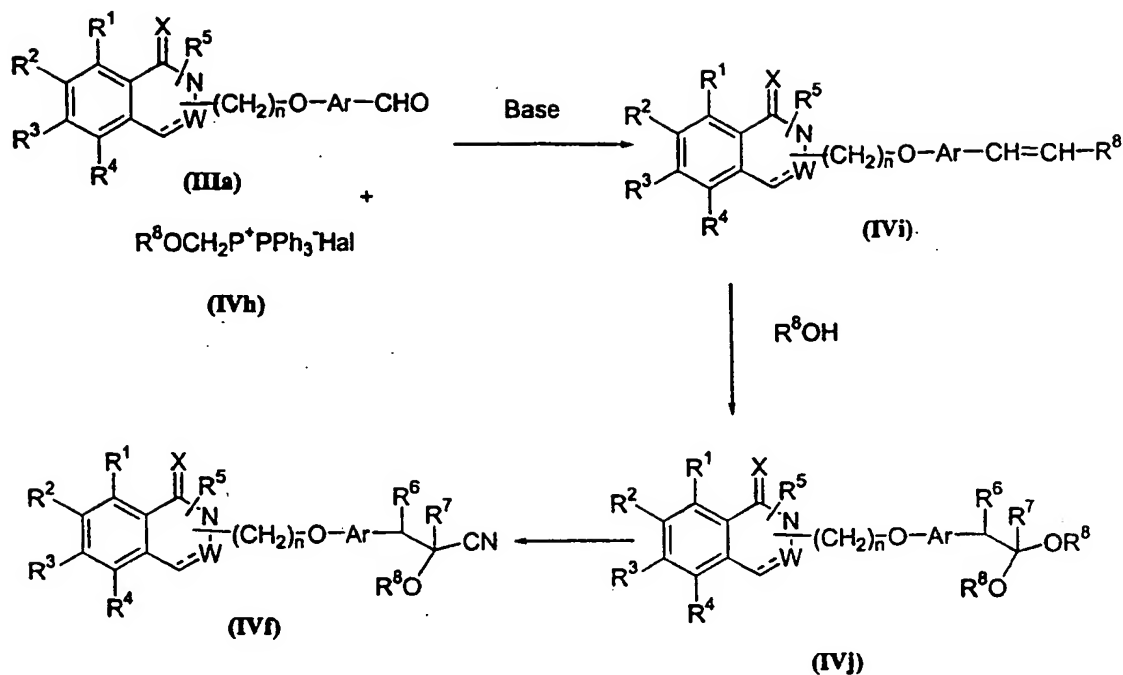


where X represents O or S; the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  may be the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy, carbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxy, carbonylamino, aralkoxy, carbonylamino, alkoxy, carbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of  $R^1$  to  $R^4$  together with the adjacent carbon atoms to which they are attached may also form a 5 to 6 membered cyclic structure carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains oxo group; “----” represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that  
 15 or its derivatives or sulfonic acid or its derivatives; any two of  $R^1$  to  $R^4$  together with the adjacent carbon atoms to which they are attached may also form a 5 to 6 membered cyclic structure carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains oxo group; “----” represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that  
 20 when W represents nitrogen atom “----” represents a bond or no bond and when W represents an oxygen atom “----” represents no bond;  $R^5$  when present on a carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy, carbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxy, carbonylamino, aralkoxy, carbonylamino, alkoxy, carbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of  $R^1$  to  $R^4$  together with the adjacent carbon atoms to which they are attached may also form a 5 to 6 membered cyclic structure carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains oxo group; “----” represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that  
 25 when W represents nitrogen atom “----” represents a bond or no bond and when W represents an oxygen atom “----” represents no bond;  $R^5$  when present on a carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy, carbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxy, carbonylamino, aralkoxy, carbonylamino, alkoxy, carbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of  $R^1$  to  $R^4$  together with the adjacent carbon atoms to which they are attached may also form a 5 to 6 membered cyclic structure carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains oxo group; “----” represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that



or its derivatives or sulfonic acid or its derivatives;  $R^5$  when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents an unsubstituted or substituted divalent single or fused aromatic or heterocyclic group;  $R^6$  represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group  $R^7$ ;  $R^7$  represents hydrogen, hydroxy, alkoxy, halogen, acyl, lower alkyl group or unsubstituted or substituted aralkyl or  $R^7$  forms a bond together with  $R^6$ ;  $R^8$  represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl group and the linker group represented by  $-(CH_2)_n-O-$  is attached either through nitrogen atom or through carbon atom, where  $n$  is an integer ranging from 1-4, a process for its preparation and its use in the preparation of  $\beta$ -aryl- $\alpha$ -substituted hydroxyalkanoic acids.

The compound of formula (IVf) where  $R^6$  and  $R^7$  each represent hydrogen atoms and all other symbols are as defined earlier is prepared by a process outlined in Scheme-III.



Scheme III

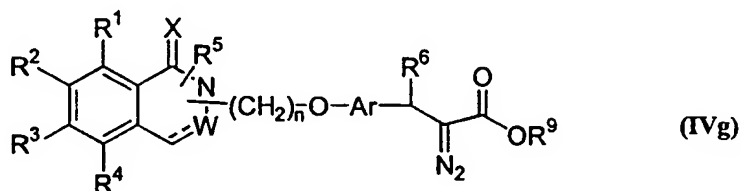
The reaction of a compound of formula (IIIa) where all symbols are as defined earlier with a compound of formula (IVh) where  $R^8$  is as defined earlier excluding hydrogen and Hal represent a halogen atom such as Cl, Br or I to produce a compound of formula (IVi) may be carried out under conventional conditions in the presence of a base. The base is not critical. Any base normally employed for Wittig reaction may be employed, metal hydride such as NaH or KH; metal alkoxides such as NaOMe,  $K^tBuO$  or NaOEt; metal amides such as  $LiNH_2$  or  $LiN(iPr)_2$ . Aprotic solvent such as THF, DMSO, dioxane, DME and the like may be used. Mixture of solvents may be used. HMPA may be used as cosolvent. Inert atmosphere may be employed such as argon and the reaction is more effective under anhydrous conditions. Temperature in the range of -80 °C to 100 °C may be used.

The compound of (IVi) where all symbols are as defined earlier and  $R^8$  is as defined earlier excluding hydrogen may be converted to a compound of formula (IVj) where  $R^6$  and  $R^7$  represent hydrogen atoms and all other symbols are as defined earlier, by treating with an alcohol of formula  $R^8OH$  where  $R^8$  represents unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl,

alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl under anhydrous conditions in the presence of a strong anhydrous acid such as p-toluenesulfonic acid.

The compound of formula (IVj) defined above upon treatment with trialkylsilyl cyanide such as trimethylsilyl cyanide produces a compound of formula (IVf) where R<sup>6</sup> and R<sup>7</sup> represent hydrogen atoms, R<sup>8</sup> is as defined earlier excluding hydrogen and all other symbols are as defined earlier.

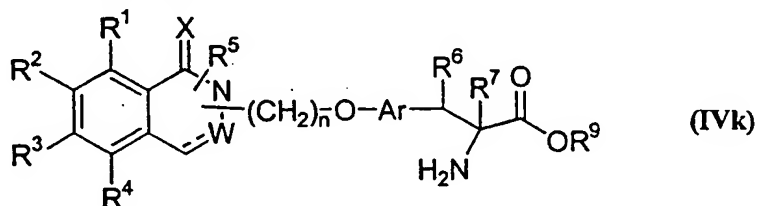
In still another embodiment of the present invention the novel intermediate of formula (IVg)



wherein X represents O or S; the groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> may be the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of R<sup>1</sup> to R<sup>4</sup> together with the adjacent carbon atoms to which they are attached may also form a 5-6 membered cyclic structure containing carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains an oxo group; “----” represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that when W represents nitrogen atom, “----” represents a bond or no bond and when W represents an oxygen atom “----” represents no bond; R<sup>5</sup> when present on carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy,

heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy, carbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxy, carbonylamino, aralkoxy, carbonylamino, 5 alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives;  $R^5$  when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, 10 monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxy, carbonyl, aralkoxy, carbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group;  $R^6$  represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or substituted aralkyl group;  $R^9$  represents hydrogen or unsubstituted or substituted groups 15 selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; and the linker group represented by  $-(CH_2)_n-O-$  is attached either through nitrogen atom or through carbon atom, where n is an integer ranging from 1-4 and a process for its preparation and its use in the preparation of  $\beta$ -aryl- $\alpha$ -substituted 20 hydroxyalkanoic acids is provided.

The compound of formula (IVg) where all other symbols are as defined earlier may be prepared by reacting a compound of formula (IVk)



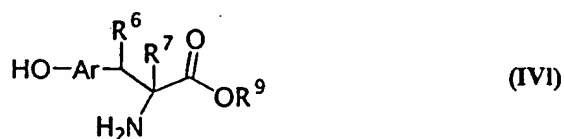
where  $R^7$  is hydrogen atom and all other symbols are as defined earlier, with an 25 appropriate diazotizing agent.

The diazotization reaction may be under conventional conditions. A suitable diazotizing agent is an alkyl nitrile, such as iso-amyl nitrile. The reaction may be carried out in presence of solvents such as THF, dioxane, ether, benzene and the like or a

combination thereof. Temperature in the range of  $-50^{\circ}\text{C}$  to  $80^{\circ}\text{C}$  may be used. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as  $\text{N}_2$ , Ar or He. The duration of the reaction may range from 1 to 24 h, preferably, 1 to 12 h.

5

The compound of formula (IVk) may also be prepared by a reaction between (IIIe) where all symbols are as defined earlier and a compound of formula (IVl)



where  $\text{R}^7$  is hydrogen atom and all other symbols are as defined earlier.

10 The reaction of compound of formula (IIIe) where all symbols are as defined earlier and a compound of formula (IVl) where all symbols are as defined earlier may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which is maintained by using inert gases such as  $\text{N}_2$ , Ar or He. The reaction may be effected in  
15 the presence of a base such as  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$  or NaH or mixtures thereof. Acetone may be used as a solvent when  $\text{K}_2\text{CO}_3$  or  $\text{Na}_2\text{CO}_3$  is used as a base. The reaction temperature may range from  $20^{\circ}\text{C}$  -  $120^{\circ}\text{C}$ , preferably at a temperature in the range of  $30^{\circ}\text{C}$  -  $80^{\circ}\text{C}$ . The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 12 hours.

20 The pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol and the like. Mixture of solvents may be used. Preparation of  
25 pharmaceutically acceptable salts of organic bases may be prepared by treatment with organic bases like lysine, arginine, glycine, guanidine, diethanolamine, choline, guanidine and their derivatives. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric

acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of  
5 solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional  
10 methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques *et al* in "Enantiomers, Racemates and Resolution" (Wiley  
15 Interscience, 1981). More specifically the compound of formula (I) where  $YR^9$  represents OH may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the  
20 stereoisomers of compound of formula (I) may be prepared by hydrolyzing the pure diastereomeric amide.

Various polymorphs of compound of general formula (I) forming part of this invention may be prepared by crystallization of compound of formula (I) under different conditions. For example, polymorphs may be prepared by using different solvents  
25 commonly used or their mixtures for recrystallization; crystallizations at different temperatures; or various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning  
30 calorimetry, powder X-ray diffraction or such other techniques.

The present invention also provides a pharmaceutical composition, containing the compounds of the general formula (I), as defined above, their derivatives, their

analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like, useful for the treatment and / or prophylaxis of diseases such as hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases and related disorders. These compounds are useful for the treatment of familial hypercholesterolemia, hypertriglyceridemia, lowering of atherogenic lipoproteins, VLDL and LDL. The compounds of the present invention can be used for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy. The compounds of general formula (I) are also useful for the treatment / prophylaxis of insulin resistance (type II diabetes), leptin resistance, impaired glucose tolerance, dyslipidemia, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease, and other cardiovascular disorders. These compounds may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and for the treatment of cancer. The compounds of the present inventions are useful in the treatment and / or prophylaxis of the above said diseases in combination / concomittant with one or more HMG CoA reductase inhibitors, hypolipidemic / hypolipoproteinemic agents such as fibric acid derivatives, nicotinic acid, cholestyramine, colestipol, probucol. The compounds of the present invention in combination with HMG CoA reductase inhibitors, hypolipidemic / hypolipoproteinemic agents can be administered together or within such a period to act synergistically. The HMG CoA reductase inhibitors may be selected from those used for the treatment or prevention of hyperlipidemia such as lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin and their analogs thereof. Suitable fibric acid derivative may be gemfibrozil, clofibrate, fenofibrate, ciprofibrate, benzaifibrate and their analogs thereof.

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, and may contain flavourants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in

suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 20 %, preferably 1 to 10 % by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

5       The compound of the formula (I) as defined above are clinically administered to mammals, including man, *via* either oral or parenteral routes. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired, as by disease or  
10 other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.01 to about 50 mg / kg body weight of the subject per day or preferably about 0.01 to about 30 mg / kg body weight per day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for  
15 treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage.

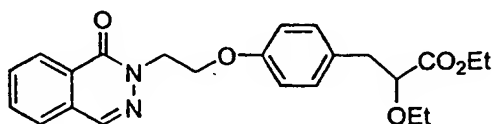
Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in  
20 the range as described above. Thus, for oral administration, the compounds can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavourants, sweeteners, excipients and the like. For parenteral administration, the compounds can be combined  
25 with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously,  
30 or intramuscularly, with intramuscular administration being preferred in humans.



The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

### 5 Example 1

(±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate

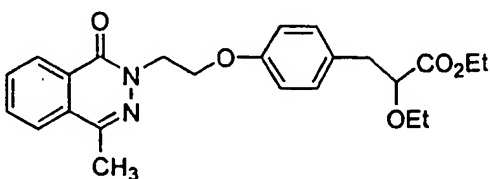


To a stirred solution of ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate (D. Haigh, 10 *Tetrahedron*, 1994, 50, 3177) (7.6 g, 31.0 mmol) in dry N,N-dimethyl formamide (40 mL) was added anhydrous potassium carbonate (7.10 g, 52.0 mmol) and stirred at about 25 °C for 20 minutes and then was added 2-(2-bromoethyl)-1(2H)phthalazinone [M. Yamaguchi; K. Kamei; T. Koga; T. Kuroki; N. Ohi, *J. Med. Chem.* 1993, 36, 4052-60] (6.2 g, 24.0 mmol) in 40 mL of dry DMF. The reaction mixture was stirred at 50 °C for 15 24 h; then it was cooled to about 25 °C and filtered. The filtrate was diluted with ethyl acetate (300 mL) and washed with water (3 x 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude compound was chromatographed over silica gel column using chloroform as eluent to obtain the title compound as an oil, (4.5 g, 45 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 8.43 (d, J = 6.65 Hz, 1H), 8.17 (s, 1H), 7.80 - 7.60 (m, 3H), 7.11 (d, J = 8.30 Hz, 2H), 6.83 (d, J = 8.30 Hz, 2H), 4.63 (t, J = 5.80 Hz, 2H), 4.38 (t, J = 5.80 Hz, 2H), 4.12 (q, J = 7.00 Hz, 2H), 3.93 (t, J = 6.60 Hz, 1H), 3.65 - 3.45 (m, 1H), 3.40 - 3.20 (m, 1H), 2.91 (d, J = 6.60 Hz, 2H), 1.30 - 1.10 (m, 6H).

### Example 2

25 (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyl)ethoxy]phenyl]propanoate

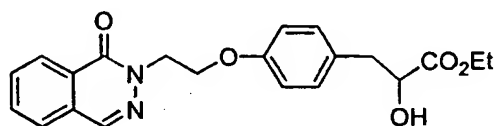


The title compound (0.5 g, 32 %) was prepared as an oil from 2-(2-bromoethyl)-4-methyl-1(2H)phthalazinone (1.0 g, 3.7 mmol), ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate (0.89 g, 3.7 mmol) and anhydrous  $K_2CO_3$  (1.0 g, 7.4 mmol) by a similar procedure to that described in example 1.

- 5  $^1H$  NMR ( $CDCl_3$ , 200 MHz):  $\delta$  8.47 (d,  $J$  = 7.98 Hz, 1H), 7.90 - 7.70 (m, 3H), 7.12 (d,  $J$  = 8.40 Hz, 2H), 6.85 (d,  $J$  = 8.40 Hz, 2H), 4.60 (t,  $J$  = 5.90 Hz, 2H), 4.39 (t,  $J$  = 5.90 Hz, 2H), 4.15 (q,  $J$  = 7.06 Hz, 2H), 3.91 (t,  $J$  = 6.65 Hz, 1H), 3.65 - 3.25 (m, 2H), 2.93 (d,  $J$  = 6.65 Hz, 2H), 2.60 (s, 3H), 1.40 - 1.10 (m, 6H).

### Example 3

- 10 ( $\pm$ ) Ethyl 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate

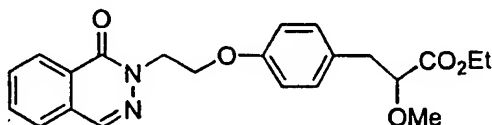


- The title compound was obtained as an oil (1.0 g, 41 %) from 2-(2-bromoethyl)-1(2H)phthalazinone (1.63 g, 6.4 mmol), ethyl 2-hydroxy-3-(4-hydroxyphenyl)propanoate (DE 2 625 163) (1.35 g, 6.4 mmol) and anhydrous potassium carbonate (1.8 g, 12.8 mmol) by a similar procedure to that described in example 1.

- $^1H$  NMR ( $CDCl_3$ , 200 MHz):  $\delta$  8.44 (d,  $J$  = 6.55 Hz, 1H), 8.18 (s, 1H), 7.9 - 7.65 (m, 3H), 7.14 (d,  $J$  = 8.30 Hz, 2H), 6.84 (d,  $J$  = 8.30 Hz, 2H), 4.63 (t,  $J$  = 5.81 Hz, 2H), 4.39 (t,  $J$  = 5.81 Hz, 2H), 4.32 (m, 1H), 4.18 (q,  $J$  = 7.24 Hz, 2H), 3.00 (dd,  $J$  = 4.56 Hz, 16.60 Hz, 1H), 2.80 (dd,  $J$  = 16.60 Hz, 4.56 Hz, 1H), 2.71 (d,  $J$  = 6.00 Hz, 1H,  $D_2O$  exchangeable), 1.26 (t,  $J$  = 7.24 Hz, 3H).

### Example 4

- ( $\pm$ ) Ethyl 2-methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate



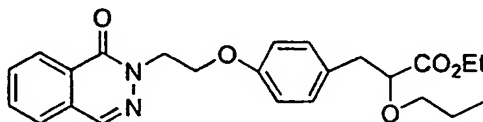
- 25 To NaH (95 %) (47 mg, 1.95 mmol) suspended in dry N,N-dimethyl formamide (5 mL) was added ethyl 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate (obtained from example 3) (0.5 g, 1.3 mmol) in

dry DMF (10 mL). The mixture was stirred under an inert atmosphere of N<sub>2</sub> for 10 minutes and methyl iodide (0.74 g, 5.2 mmol) was added. The reaction mixture was stirred at about 25 °C for 24 h. The reaction was quenched with ice and extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with excess of water and  
 5 with brine. The combined extract was dried over anhydrous sodium sulfate and the solvent was evaporated to give an oil, which was chromatographed on silica gel column by eluting with 1:4 ethyl acetate : pet. ether to give an oily compound. (yield : 0.18 g, 35 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.43 (d, J = 8.48 Hz, 1H), 8.19 (s, 1H), 7.90 - 7.67  
 10 (m, 3H), 7.10 (d, J = 8.49 Hz, 2H), 6.85 (d, J = 8.49 Hz, 2H), 4.64 (t, J = 5.91 Hz, 2H), 4.39 (t, J = 5.91 Hz, 2H), 4.16 (q, J = 7.47 Hz, 2H), 3.88 (t, J = 5.81 Hz, 1H), 3.32 (s, 3H), 2.92 (d, J = 5.81 Hz, 2H), 1.21 (t, J = 7.47 Hz, 3H).

#### Example 5

(±) Ethyl-2-propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]  
 15 propanoate

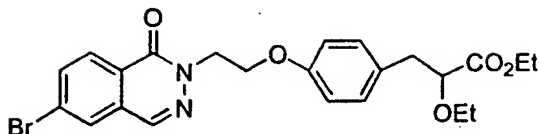


The title compound (0.21 g, 95 %) was obtained as a gummy liquid from (±) ethyl 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate (obtained from example 3) (0.2 g, 0.52 mmol) and 1-bromopropane (0.32 g, 2.62 mmol) by a  
 20 similar procedure to that described in example 4.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.46 (d, J = 6.64 Hz, 1H), 8.20 (s, 1H), 7.90 - 7.70 (m, 3H), 7.11 (d, J = 8.62 Hz, 2H), 6.87 (d, J = 8.62 Hz, 2H), 4.66 (t, J = 5.72 Hz, 2H), 4.41 (t, J = 5.72 Hz, 2H), 4.30 - 4.08 (m, 5H), 3.05 (dd, J = 4.57 Hz, J = 14.11 Hz, 1H), 2.89 (dd, J = 6.55 Hz, 14.11 Hz, 1H), 1.80 - 1.10 (m, 2H), 1.27 (t, J = 7.06 Hz,  
 25 3H), 0.95 (t, J = 7.42 Hz, 3H).

#### Example 6

(±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]propanoate

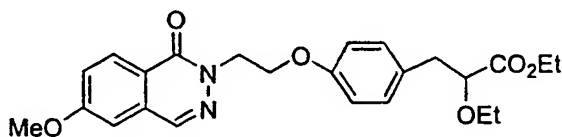


To a stirred suspension of NaH (95 %, 72 mg, 3.0 mmol) in dry DMF (2 mL) was added 6-bromo-1(2H)phthalazinone [P. Consonni, A. Omodei, -Sale; Farmaco., Ed. Sci., 1976, 31, 691 - 703 ; The Chemistry of Heterocyclic compounds; condensed pyridazines including cinnolines and phthalazines., ed. R. N Castle.; John Willey and Sons. 1973, 27, 375 - 441] (0.45 g, 2.0 mmol) in dry DMF (3 mL) at 0 °C. The reaction mixture was stirred at about 25 °C for 0.5 h. Ethyl 2-ethoxy-[4-(2-bromoethoxy)phenyl]propanoate (prepared as disclosed in patent application 09/012,585) (0.76 g, 2.2 mmol) in dry DMF (3 mL) was added and the reaction mixture was stirred at about 25 °C for 4 h. Ice was added to the reaction mixture and stirred for 0.5 h. The mixture was extracted with ethyl acetate (2 x 200 mL). The combined ethyl acetate layers were washed with water (3 x 100 mL) and then with brine ; dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated the solvent. The crude compound was chromatographed over silica gel using 3:7 EtoAc : Pet.Ether as eluent to obtain the title compound as a gummy oil (0.47 g, 50 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.30 (d, J = 9.13 Hz, 1H), 8.10 (s, 1H), 7.88 - 7.85 (m, 2H), 7.12 (d, J = 8.63 Hz, 2H), 6.83 (d, J = 8.63 Hz, 2H), 4.62 (t, J = 5.88 Hz, 2H), 4.39 (t, J = 5.88 Hz, 2H), 4.15 (q, J = 7.10 Hz, 2H), 3.94 (t, J = 6.74 Hz, 1H), 3.70 - 3.20 (m, 2H), 2.92 (d, J = 6.74 Hz, 2H), 1.20 - 1.00 (m, 6H).

#### Example 7

(±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]propanoate

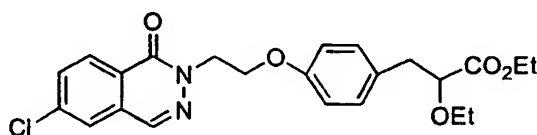


The title compound (0.28 g, 45 %) was obtained as an oil from 6-methoxy-1(2H)phthalazinone (0.25 g, 1.42 mmol), ethyl 2-ethoxy-[4-(2-bromoethoxy)phenyl]propanoate (0.54 g, 1.56 mmol) and NaH (95 %, 55 mg, 2.13 mmol) by a similar procedure to that described in example 6.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 8.36 (d, J = 8.81 Hz, 1H), 8.11 (s, 1H), 7.71 (d, J = 8.81 Hz, 1H), 7.35 - 7.25 (m, 1H), 7.13 (d, J = 8.40 Hz, 2H), 6.85 (d, J = 8.40 Hz, 2H), 4.62 (t, J = 5.49 Hz, 2H), 4.45 (t, J = 5.49 Hz, 2H), 4.25 (t, J = 6.65 Hz, 1H), 4.15 (q, J = 7.15 Hz, 2H), 3.95 (s, 3H), 3.70 - 3.20 (m, 2H), 2.93 (d, J = 6.65 Hz, 2H), 1.40 - 1.15 (m, 6H).

#### Example 8

(±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]propanoate

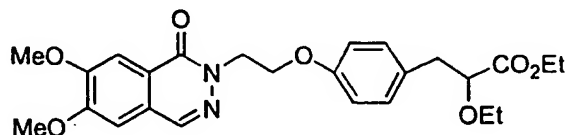


The title compound (0.58 g, 50 %) was obtained as an oil from 6-chloro-1(2H)phthalazinone (0.45 g, 2.50 mmol), ethyl 2-ethoxy-[4-(2-bromoethoxy)phenyl]propanoate (0.94 g, 2.74 mmol) and NaH (95 %, 0.1 g, 3.75 mmol) by a similar procedure to that described in example 6.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 8.37 (d, J = 7.39 Hz, 1H), 8.16 (s, 1H), 7.80 - 7.60 (m, 2H), 7.12 (d, J = 8.39 Hz, 2H), 6.82 (d, J = 8.39 Hz, 2H), 4.63 (t, J = 5.82 Hz, 2H), 4.39 (t, J = 5.82 Hz, 2H), 4.10 (q, J = 7.15 Hz, 2H), 3.94 (t, J = 6.55 Hz, 1H), 3.70 - 3.20 (m, 2H), 2.92 (d, J = 6.55 Hz, 2H), 1.30 - 1.10 (m, 6H).

#### Example 9

(±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]propanoate



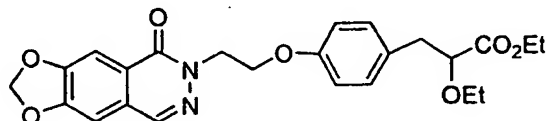
The title compound (0.52 g, 50 %) was obtained as an oil from 6,7-dimethoxy-1(2H)phthalazinone (0.5 g, 2.43 mmol), ethyl 2-ethoxy-[4-(2-bromoethoxy)phenyl]propanoate (92 mg, 2.67 mmol) and NaH (95 %, 95 mg, 3.64 mmol) by a similar procedure to that described in example 6.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 8.08 (s, 1H), 7.79 (s, 1H), 7.16 (d, J = 8.72 Hz, 2H), 7.01 (s, 1H), 6.84 (d, J = 8.72 Hz, 2H), 4.63 (t, J = 5.81 Hz, 2H), 4.39 (t, J = 5.81 Hz,

2H), 4.12 (q,  $J = 7.20$  Hz, 2H), 4.05 (s, 3H), 4.03 (s, 3H), 3.94 (t,  $J = 6.65$  Hz, 1H), 3.70 - 3.20 (m, 2H), 2.92 (d,  $J = 6.65$  Hz, 2H), 1.25 - 1.10 (m, 6H).

#### Example 10

(±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]phenyl]propanoate

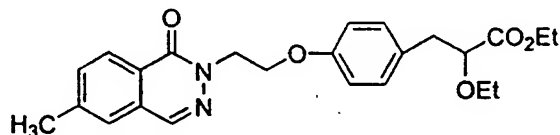


The title compound (0.38 g, 54 %) was obtained as an oil from 6,7-(1,3)-dioxolo-1(2H)phthalazinone (0.3 g, 1.57 mmol), ethyl 2-ethoxy-[4-(2-bromoethoxy)phenyl]propanoate (0.6 g, 1.73 mmol) and NaH (95 %, 60 mg, 2.35 mmol) by a similar procedure to that described in example 6.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz):  $\delta$  8.0 (s, 1H), 7.75 (s, 1H), 7.11 (d,  $J = 8.72$  Hz, 2H), 6.98 (s, 1H), 6.83 (d,  $J = 8.72$  Hz, 2H), 6.16 (s, 2H), 4.61 (t,  $J = 5.63$  Hz, 2H), 4.34 (t,  $J = 5.63$  Hz, 2H), 4.23 (q,  $J = 7.11$  Hz, 2H), 3.94 (t,  $J = 6.92$  Hz, 1H), 3.70 - 3.20 (m, 2H), 2.92 (d,  $J = 6.92$  Hz, 2H), 1.4 - 1.15 (m, 6H).

#### Example 11

(±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]propanoate

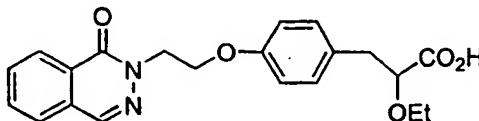


The title compound was obtained (0.8 g, 43 %) as an oil from 6-methyl-1(2H)phthalazinone (0.71 g, 4.43 mmol), ethyl 2-ethoxy-[4-(2-bromoethoxy)phenyl]propanoate (1.83 g, 5.3 mmol) and NaH (95 %, 0.17 g, 6.84 mmol) by a similar procedure to that described in example 6.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz):  $\delta$  8.32 (d,  $J = 7.98$  Hz, 1H), 8.12 (s, 1H), 7.59 (d,  $J = 7.98$  Hz, 1H), 7.48 (s, 1H), 7.12 (d,  $J = 8.39$  Hz, 2H), 6.84 (d,  $J = 8.39$  Hz, 2H), 4.63 (t,  $J = 5.81$  Hz, 2H), 4.39 (t,  $J = 5.81$  Hz, 2H), 4.15 (q,  $J = 7.06$  Hz, 2H), 3.94 (t,  $J = 6.65$  Hz, 1H), 3.63 - 3.29 (m, 2H), 2.92 (d,  $J = 6.65$  Hz, 2H), 2.55 (s, 3H), 1.30 - 1.18 (m, 6H).

#### Example 12

(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid

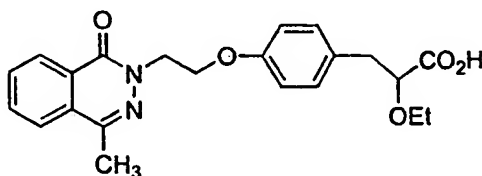


To a stirred methanolic solution (60 mL) of (±) ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate (obtained from example 1, 4.0 g, 9.0 mmol) was added aqueous sodium carbonate solution (10.0 g in 60 mL of water) at about 25 °C for hydrolysis of ester. After 24 h, methanol was evaporated under reduced pressure. The aqueous layer was diluted with water (50 mL) and washed with ethyl acetate (2 x 100 mL). The aqueous layer was acidified with dilute HCl (6N) and extracted with ethyl acetate. The extracts were washed with water and then with brine; dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated to obtain a liquid which slowly became a white solid, m.p. 111 °C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 8.44 (d, J = 7.00 Hz, 1H), 8.18 (s, 1H), 7.79 - 7.67 (m, 3H), 7.11 (d, J = 8.30 Hz, 2H), 6.84 (d, J = 8.30 Hz, 2H), 4.63 (t, J = 5.80 Hz, 2H), 4.39 (t, J = 5.80 Hz, 2H), 4.04 - 3.98 (m, 1H), 3.62 - 3.35 (m, 2H), 3.07 (dd, J = 4.10 Hz, 14.10 Hz, 1H), 2.91 (dd, J = 7.40 Hz, 14.10 Hz, 1H), 1.14 (t, J = 7.0 Hz, 3H).

**Example 13**

(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyl)ethoxy]phenyl]propanoic acid



20

The title compound (0.4 g, 86 %) was obtained as a sticky oil from (±) ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyl)ethoxy]phenyl]propanoate (obtained from example 2) (0.5 g, 1.18 mmol) and aqueous Na<sub>2</sub>CO<sub>3</sub> (0.52 g, 4.72 mmol in 8 mL of water) by a procedure similar to that described in example 12.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 8.46 (d, J = 7.56 Hz, 1H), 7.90 - 7.70 (m, 3H), 7.12 (d, J = 8.39 Hz, 2H), 6.85 (d, J = 8.39 Hz, 2H), 4.60 (t, J = 5.90 Hz, 2H), 4.39 (t, J = 5.90 Hz, 2H), 4.05 - 3.95 (m, 1H), 3.65 - 3.35 (m, 2H), 3.02 (dd, J = 7.47 Hz, 17.11

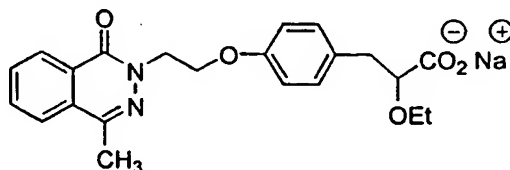
25

Hz, 1H), 2.85 (dd,  $J = 7.47$  Hz, 17.11 Hz, 1H), 2.59 (s, 3H), 1.15 (t,  $J = 6.82$  Hz, 3H).

#### Example 14

(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyl)ethoxy]phenyl]

5 propanoic acid sodium salt

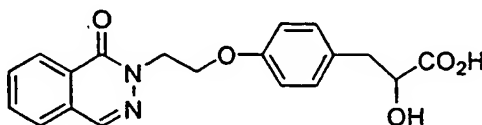


To an ether solution (10 mL) of (±) 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyl)ethoxy]phenyl]propanoic acid (0.25 g, 0.63 mmol) (obtained from example 13) was added 0.16 mL of 11 % sodium methoxide solution in methanol. After stirring at about 25 °C for one hour, the reaction mixture was diluted with ether (20 mL) and the white precipitate filtered off which was washed with 2 % methanolic ether and dried under reduced pressure for 12 h to obtain a white solid (0.2 g, 77 %) m.p: 124 °C.

1H NMR (DMSO- $d_6$ ):  $\delta$  8.33 (d,  $J = 7.47$  Hz, 1H), 8.0 - 7.80 (m, 3H), 7.10 (d,  $J = 8.40$  Hz, 2H), 6.79 (d,  $J = 8.40$  Hz, 2H), 4.48 (t,  $J = 4.98$  Hz, 2H), 4.34 (t,  $J = 4.98$  Hz, 2H), 3.60 - 3.40 (m, 1H), 3.30 - 3.05 (m, 2H), 2.90 (dd,  $J = 7.47$  Hz, 17.11 Hz, 1H), 2.79 (dd,  $J = 7.47$  Hz, 17.11 Hz, 1H), 2.58 (s, 3H), 0.97 (t,  $J = 6.97$  Hz, 3H).

#### Example 15

(±) 2-Hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid



The title compound (0.68 g, 73 %) was obtained as a white solid from (±) ethyl 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate (obtained from example 3) (1.0 g, 2.62 mmol) and aqueous  $\text{Na}_2\text{CO}_3$  (2.5 g, 23.56 mmol in 30 mL of water) by a similar procedure to that described in example 12. mp : 120 °C.

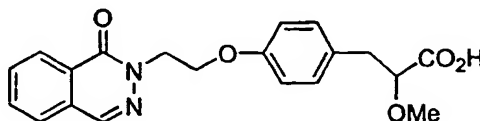
1H NMR ( $\text{CDCl}_3 + \text{DMSO } d_6$ ):  $\delta$  8.41 (d,  $J = 7.15$  Hz, 1H), 8.22 (s, 1H), 7.90 - 7.70 (m, 3H), 7.49 (s, 1H), 7.16 (d,  $J = 8.21$  Hz, 2H), 6.83 (d,  $J = 8.21$  Hz, 2H), 4.62 (t,  $J = 5.30$  Hz, 2H), 4.39 (t,  $J = 5.30$  Hz, 2H) 4.30 - 4.20 (m, 1H), 3.8 (bs, 1H,  $\text{D}_2\text{O}$ )



exchangeable), 3.05 (dd,  $J = 2.07$  Hz, 14.11 Hz, 1H), 2.83 (dd,  $J = 7.15$  Hz, 14.11 Hz, 1H).

#### Example 16

(±) 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid

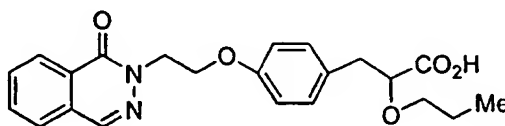


The title compound (0.1 g, 60 %) was obtained as a white solid from (±) ethyl 2-methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate (obtained from example 4) (0.18 g, 0.45 mmol) by hydrolysis with aqueous sodium carbonate (0.24 g, 2.27 mmol) by a similar procedure to that described in example 12.  
mp : 140 °C.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz) :  $\delta$  8.42 (d,  $J = 8.62$  Hz, 1H), 8.17 (s, 1H), 7.85 - 7.65 (m, 3H), 7.10 (d,  $J = 8.62$  Hz, 2H), 6.83 (d,  $J = 8.62$  Hz, 2H), 4.62 (t,  $J = 5.81$  Hz, 2H), 4.38 (t,  $J = 5.81$  Hz, 2H), 4.00 - 3.90 (m, 1H), 3.35 (s, 3H), 3.02 (dd,  $J = 4.48$  Hz, 12.87 Hz, 1H), 2.89 (dd,  $J = 9.47$  Hz, 12.87 Hz, 1H), 2.62 (bs, 1H,  $\text{D}_2\text{O}$  exchangeable).

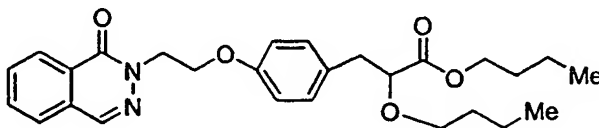
#### Example 17

(±) 2-Propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid



The title compound (80 mg, 40 %) was obtained as a gummy liquid from (±) ethyl 2-propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]propanoate (obtained from example 5) (0.21 g, 0.495 mmol) by hydrolysis with aqueous sodium carbonate (0.26 g, 2.47 mmol) by a similar procedure to that described in example 12.

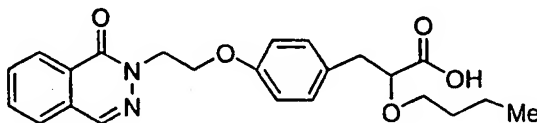
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz) :  $\delta$  8.45 (d,  $J = 6.97$  Hz, 1H), 8.18 (s, 1H), 7.90 - 7.65 (m, 3H), 7.11 (d,  $J = 8.39$  Hz, 2H), 6.84 (d,  $J = 8.39$  Hz, 2H), 4.64 (t,  $J = 5.81$  Hz, 2H), 4.40 (t,  $J = 5.81$  Hz, 2H), 4.03 - 3.99 (m, 1H), 3.60 - 3.30 (m, 2H), 3.05 (dd,  $J = 14.20$  Hz, 4.16 Hz, 1H), 2.92 (dd,  $J = 4.16$  Hz, 12.82 Hz, 1H), 2.20 (bs, 1H,  $\text{D}_2\text{O}$  exchangeable), 1.53 (q,  $J = 7.05$  Hz, 2H), 0.86 (t,  $J = 7.05$  Hz, 3H).

**Example 18****(±) Butyl 2-butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate**

- 5 To NaH (95%) (68 mg, 2.82 mmol) suspended in dry DMF (5 mL) was added (±) 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid (0.5 g, 1.41 mmol) (obtained from example 15) and stirred at about 25 °C for 20 min. n-butyl bromide (0.77 g, 5.65 mmol) was added and the reaction mixture was stirred at 60 °C for 16 h. The reaction was quenched with ice and extracted with ethyl acetate (100 mL).
- 10 The ethyl acetate layer was washed with water (3 x 20 mL) and with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated to give the compound as an oil (0.25 g, 40 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.45 (d, J = 6.97 Hz, 1H), 8.18 (s, 1H), 7.90 - 7.65 (m, 3H), 7.11 (d, J = 8.49 Hz, 2H), 6.83 (d, J = 8.49 Hz, 2H), 4.64 (t, J = 5.81 Hz, 2H), 4.39 (t, J = 5.81 Hz, 2H), 4.08 (t, J = 6.64 Hz, 2H), 3.92 (t, J = 6.36 Hz, 1H), 3.50 (m, 1H), 3.20 (m, 1H), 2.91(d, J = 6.36 Hz, 2H), 1.70 - 1.42 (m, 4H), 1.40 - 1.20 (m, 4H), 0.92 - 0.79 (m, 6H).

15

**Example 19****(±) 2-Butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid**

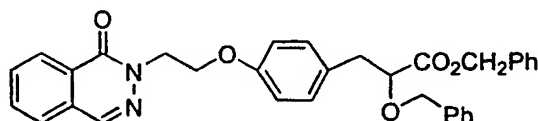
- The title compound (0.1 g, 48 %) was obtained as a gummy liquid from (±) butyl 2-butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate (0.25 g, 0.536 mmol) (obtained from example 18) by hydrolysis with aqueous Na<sub>2</sub>CO<sub>3</sub> (0.12 g, 1.08 mmol) by a similar procedure to that described in example 12.
- 25

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.44 (d, J = 8.40 Hz, 1H), 8.19 (s, 1H), 7.85 - 7.67 (m, 3H), 7.11 (d, J = 8.62 Hz, 2H), 6.83 (d, J = 8.62 Hz, 2H), 4.64 (t, J = 5.81 Hz,

2H), 4.39 (t,  $J = 5.81$  Hz, 2H), 4.02 - 3.96 (m, 1H), 3.60 - 3.25 (m, 2H), 3.05 (dd,  $J = 9.96$  Hz, 14.20 Hz, 1H), 2.94 (dd,  $J = 7.05$  Hz, 14.20 Hz, 1H), 1.60 - 1.40 (m, 2H), 1.38 - 1.15 (m, 2H), 0.83 (t,  $J = 7.15$  Hz, 3H).

#### Example 20

5 (±) Benzyl 2-benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate

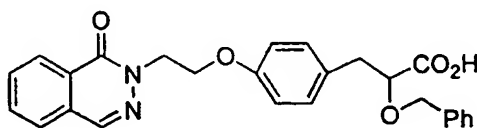


The title compound (0.21 g, 70 %) was obtained from (±) 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid (0.2 g, 0.565 mmol) (obtained from example 15), benzyl bromide (0.19 g, 1.13 mmol) and NaH (27 mg, 1.13 mmol) by a similar procedure to that described in example 18.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  8.45 (d,  $J = 8.20$  Hz, 1H), 8.22 (s, 1H), 7.90 - 7.73 (m, 3H), 7.50 - 7.14 (m, 10H), 7.08 (d,  $J = 8.63$  Hz, 2H), 6.83 (d,  $J = 8.63$  Hz, 2H), 5.15 (s, 2H), 4.73 (s, 2H), 4.65 (t,  $J = 5.81$  Hz, 2H), 4.42 (t,  $J = 5.81$  Hz, 2H), 4.12 (t,  $J = 5.26$  Hz, 1H), 3.00 (d,  $J = 5.26$  Hz, 2H).

#### Example 21

(±) 2-Benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid

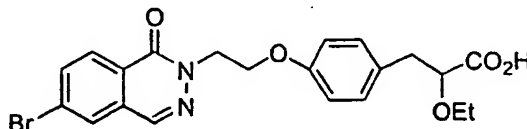


20 The title compound (0.1 g, 60 %) was obtained as a gummy liquid from (±) benzyl 2-benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate (0.2 g, 0.37 mmol) (obtained from example 20), and aqueous Na<sub>2</sub>CO<sub>3</sub> (0.24 g, 2.26 mmol) by hydrolysis as described in example 12.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  8.42 (d,  $J = 8.64$  Hz, 1H), 8.21 (s, 1H), 7.90 - 7.73 (m, 3H), 7.30 - 7.18 (m, 5H), 7.13 (d,  $J = 8.62$  Hz, 2H), 6.87 (d,  $J = 8.62$  Hz, 2H), 4.64 (t,  $J = 4.75$  Hz, 2H), 4.57 (s, 2H), 4.43 (t,  $J = 4.75$  Hz, 2H), 3.10 (dd,  $J = 4.24$  Hz, 14.12 Hz, 1H), 2.95 (dd,  $J = 5.76$  Hz, 14.12 Hz, 1H), 2.70 (bs, 1H, D<sub>2</sub>O exchangeable).

#### Example 22

**(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]propanoic acid**

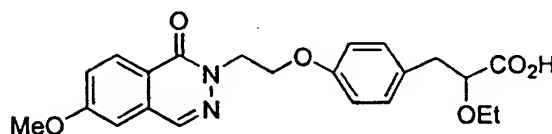


The title compound (0.18 g, 50 %) was obtained as a white solid from (±) ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]propanoate (0.38 g, 0.84 mmol) (obtained from example 6) and aqueous sodium carbonate (0.45 g, 4.19 mmol in 8 mL of H<sub>2</sub>O) by hydrolysis using a similar procedure to that described in example 12. mp: 108 - 110 °C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.31 (d, J = 9.04 Hz, 1H), 8.11 (s, 1H), 7.95 - 7.86 (m, 2H), 7.12 (d, J = 8.39 Hz, 2H), 6.84 (d, J = 8.39 Hz, 2H), 4.62 (t, J = 5.49 Hz, 2H), 4.40 (t, J = 5.49 Hz, 2H), 4.10 - 4.01 (m, 1H), 3.65 - 3.40 (m, 2H), 3.06 (dd, J = 4.15 Hz, 7.38 Hz, 1H), 2.92 (dd, J = 6.74 Hz, 7.38 Hz, 1H), 2.00 (bs, 1H, D<sub>2</sub>O exchangeable), 1.17 (t, J = 6.96 Hz, 3H).

**Example 23**

**(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]propanoic acid**

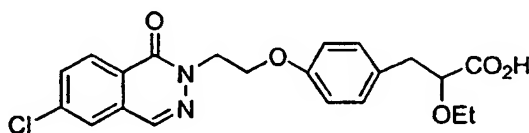


The title compound (0.12 g, 48 %) was obtained as a white solid from (±) ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]propanoate (0.27 g, 0.61 mmol) (obtained from example 7) and aqueous sodium carbonate (0.45 g, 0.1 mmol) by hydrolysis using a similar procedure to that described in example 12, mp: 142- 144 °C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.36 (d, J = 8.81 Hz, 1H), 8.12 (s, 1H), 7.33 (d, J = 8.81 Hz, 1H), 7.13 (d, J = 8.39 Hz, 2H), 7.04 (s, 1H), 6.86 (d, J = 8.39 Hz, 2H), 4.63 (t, J = 5.49 Hz, 2H), 4.40 (t, J = 5.49 Hz, 2H), 4.10 - 4.00 (m, 1H), 3.96 (s, 3H), 3.60 - 3.40 (m, 2H), 3.09 (dd, J = 4.06 Hz, 14.80 Hz, 1H), 2.90 (dd, J = 7.38 Hz, 14.80 Hz, 1H), 1.17 (t, J = 6.96 Hz, 3H).

**Example 24**

**(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyloxy)]phenyl]propanoic acid**

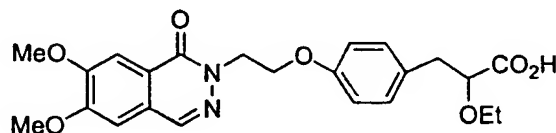


5 The title compound (0.43 g, 81 %) was obtained as a white solid from (±) ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyloxy)]phenyl]propanoate (0.57 g, 1.28 mmol) (obtained from example 8) and aqueous sodium carbonate (0.69 g, 6.4 mmol) by hydrolysis using a similar procedure to that described in example 12, mp : 92 - 94 °C.

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.37 (d, J = 8.62 Hz, 1H), 8.16 (s, 1H), 7.80 - 7.60 (m, 2H), 7.11 (d, J = 8.39 Hz, 2H), 6.83 (d, J = 8.39 Hz, 2H), 4.63 (t, J = 5.40 Hz, 2H), 4.39 (t, J = 5.40 Hz, 2H), 4.06 - 4.02 (m, 1H), 3.65 - 3.35 (m, 2H), 3.05 (dd, J = 4.16 Hz, 14.12 Hz, 1H), 2.90 (dd, J = 7.25 Hz, 14.12 Hz, 1H), 1.16 (t, J = 7.06 Hz, 3H).

**Example 25**

**(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyloxy)]phenyl]propanoic acid**



20 The title compound (0.2 g, 52 %) was obtained as a cream coloured solid from (±) ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyloxy)]phenyl]propanoate (0.25 g, 0.53 mmol) (obtained from Example 9) and aqueous sodium carbonate (0.28 g, 2.65 mmol) by hydrolysis using a similar procedure to that described in example 12. mp : 188 - 192 °C.

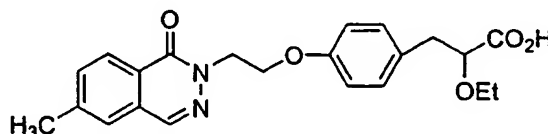
25 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.08 (s, 1H), 7.78 (s, 1H), 7.12 (d, J = 8.58 Hz, 2H), 7.01 (s, 1H), 6.85 (d, J = 8.58 Hz, 2H), 4.60 (t, J = 5.72 Hz, 2H), 4.39 (t, J = 5.72 Hz, 2H), 4.04 (s, 3H), 4.02 (s, 3H), 3.6 - 3.4 (m, 2H), 3.05 (dd, J = 4.60 Hz, 18.50 Hz,

1H), 2.91 (dd,  $J = 7.40$  Hz,  $18.50$  Hz, 1H), 2.50 (bs, 1H,  $D_2O$  exchangeable), 1.16 (t,  $J = 7.06$  Hz, 3H).

#### Example 26

(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]

5 phenyl]propanoic acid

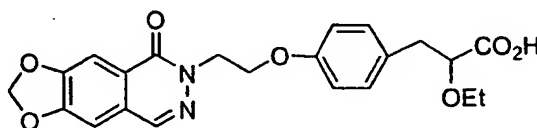


The title compound (0.56 g, 76 %), was obtained as a white solid from (±) ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]propanoate (obtained from example 11) (0.8 g, 1.88 mmol) and aqueous  $Na_2CO_3$  (1.01 g, 9.43 mmol) in 8 mL of  $H_2O$ ) by hydrolysis using a similar procedure to that described in example 12, m.p.  $100 - 102$  °C.

$^1H$  NMR ( $CDCl_3$ , 200 MHz) :  $\delta$  8.34 (d,  $J = 8.21$  Hz, 1H), 8.14 (s, 1H), 7.60 (d,  $J = 8.21$  Hz, 1H), 7.50 (s, 1H), 7.14 (d,  $J = 8.30$  Hz, 2H), 6.86 (d,  $J = 8.30$  Hz, 2H), 5.00 (bs, 1H,  $D_2O$  exchangeable), 4.64 (t,  $J = 5.81$  Hz, 2H), 4.40 (t,  $J = 5.81$  Hz, 2H), 4.10 - 4.00 (m, 15 1H), 3.63 - 3.38 (m, 2H), 3.06 (dd,  $J = 4.15$  Hz,  $14.11$  Hz, 1H), 2.92 (dd,  $J = 7.5$  Hz,  $14.11$  Hz, 1H), 2.56 (s, 3H), 1.17 (t,  $J = 6.96$  Hz, 3H).

#### Example 27

(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]phenyl]propanoic acid



20

The title compound (0.18 g, 50 %) was obtained as a white solid from (±) ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]phenyl]propanoate (0.38 g, 0.84 mmol) (obtained from example 10) and aqueous sodium carbonate (0.45 g, 4.19 mmol) by hydrolysis using a similar procedure to that described in example 12, m.p.  $118 - 120$  °C.

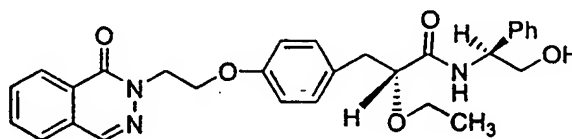
25

$^1H$  NMR ( $CDCl_3$ , 200 MHz) :  $\delta$  8.01 (s, 1H), 7.75 (s, 1H), 7.12 (d,  $J = 8.63$  Hz, 2H), 6.99 (s, 1H), 6.84 (d,  $J = 8.63$  Hz, 2H), 6.16 (s, 2H), 4.61 (t,  $J = 5.81$  Hz,

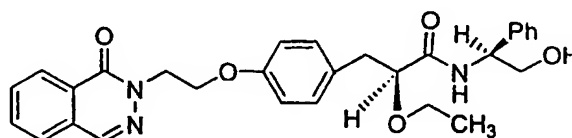
2H), 4.38 (t,  $J = 5.81$  Hz, 2H), 4.06 - 3.96 (m, 1H), 3.60 - 3.35 (m, 2H), 3.05 (dd,  $J = 4.05$  Hz, 14.11 Hz, 1H), 2.90 (dd,  $J = 7.47$  Hz, 14.11 Hz, 1H), 1.16 (t,  $J = 7.05$  Hz, 3H).

### Example 28

- 5 [2R, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (28a)



- [2S, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (28b)



10

- (±) 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid (1.0 g, 2.6 mmol) (obtained from example 12) was dissolved in 10 mL of dry dichloromethane and triethyl amine (0.52 g, 5.2 mmol) was added. The reaction mixture was cooled to 0 °C and pivaloyl chloride (0.38 mL, 3.14 mmol) was added. The reaction mixture was allowed to stir at about 25 °C for 0.5 h until all the acid was converted to mixed anhydride (checked by TLC), after which (S) (+)-2-phenyl glycinol (0.38 g, 2.88 mmol) and dry triethyl amine (0.52 g, 5.2 mmol) in dichloromethane (10 mL) were added. After stirring the reaction mixture at about 25 °C for 2 h, water was added and the mixture was extracted with dichloromethane. The organic extracts were washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue was chromatographed on silica gel using a gradient of 50 - 80 % ethyl acetate in pet. ether as eluent to afford firstly a diastereomer tentatively assigned as [(2R), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (28a) (0.38 g); followed by [(2S), N(1S)]-propanamide (28b) as a foam (0.75 g).

25

28a : m.p. 112 - 114 °C;  $[\alpha]_D^{25} = 19.8^\circ$  (c = 1, CHCl<sub>3</sub>) 98 % d.e. (by HPLC).

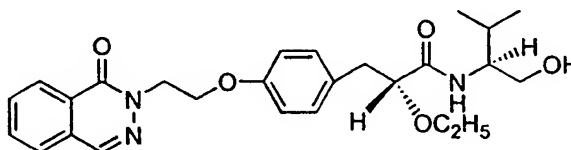
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.43 (d, 1H), 8.17 (s, 1H), 7.80 - 7.65 (m, 3H), 7.23 (d, J = 8.63 Hz, 2H), 7.19 - 7.01 (m, 5H), 6.76 (d, J = 8.63 Hz, 2H), 4.94 - 4.87 (m, 1H), 4.62 (t, J = 5.87 Hz, 2H), 4.35 (t, J = 5.87 Hz, 2H), 3.97 - 3.92 (m, 1H), 3.80 (d, J = 4.96 Hz, 2H), 3.51 - 3.45 (m, 2H), 3.06 (dd, J = 3.74 Hz, 14.14 Hz, 1H), 2.83 (dd, J = 6.64 Hz, 14.14 Hz, 1H), 1.14 (t, J = 6.96 Hz, 3H).

28b : mp : 90 - 94 °C; [α]<sub>D</sub><sup>25</sup> = -16.11 (c = 1.0; CHCl<sub>3</sub>) 97 % d.e. (by HPLC);

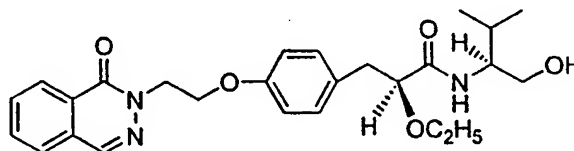
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) : δ 8.42 (d, J = 8.72 Hz, 1H), 8.17 (s, 1H), 7.80 - 7.65 (m, 3H), 7.30 - 7.10 (m, 5H), 7.03 (d, J = 8.63 Hz, 2H), 6.74 (d, J = 8.63 Hz, 2H), 4.96 - 4.87 (m, 1H), 4.63 (t, J = 5.82 Hz, 2H), 4.35 (t, J = 5.82 Hz, 2H), 4.00 - 3.90 (m, 1H), 3.81 (d, J = 4.98 Hz, 2H), 3.56 - 3.44 (m, 2H), 2.90 (dd, J = 3.74 Hz, 14.12 Hz, 1H), 2.80 (dd, J = 7.53 Hz, 14.12 Hz, 1H), 1.14 (t, J = 7.06 Hz, 3H).

#### Example 29

[(2R), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-isopropylethyl)propanamide (29a)



[(2S), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-isopropylethyl)propanamide (29b)



(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid (0.5 g, 1.31 mmol) (obtained from example 12) was dissolved in 5 mL of anhydrous dichloromethane and triethyl amine (0.33 g, 3.3 mmol) was added. The reaction mixture was cooled to 0 °C and pivaloyl chloride (0.175g, 1.44 mmol) was added. The reaction mixture was allowed to stir at room temperature for 30 min until all the acid was converted to mixed anhydride (checked by TLC), after which L(+)-valinol (0.15 g, 1.44 mmol) and dry triethylamine (0.33 g, 3.3 mmol) in 5 mL of dry dichloromethane was



added. After stirring the reaction mixture at room temperature (about 25 °C) for 4 h, water was added and the mixture was extracted with dichloromethane. The organic extracts were washed with water, brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue was chromatographed on silica gel using a gradient of 50 – 80 % ethyl acetate in pet.ether as eluent to afford firstly a diastereomer tentatively assigned as [(2R), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-isopropylethyl)propanamide (29a) (0.135 g), as a solid followed by the desired [(2S),N(1S)]-propanamide (29b) as an oil (0.12 g).

29a :  $[\alpha]_D^{25} = +8.7^\circ$  (c = 1.0; CHCl<sub>3</sub>); m.p : 80 - 82 °C.

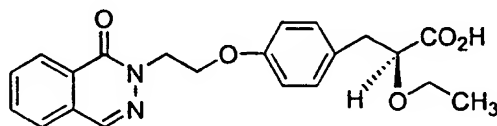
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  8.42 (d, J = 8.71 Hz, 1H), 8.19 (s, 1H), 7.82 - 7.67 (m, 3H), 7.12 (d, J = 8.63 Hz, 2H), 6.83 (d, J = 8.63 Hz, 2H), 6.54 (d, J = 8.39 Hz, 1H), 4.62 (t, J = 5.82 Hz, 2H), 4.41 (t, J = 5.82 Hz, 2H), 4.00 - 3.90 (m, 1H), 3.65 - 3.35 (m, 5H), 3.05 (dd, J = 3.74 Hz, 14.12 Hz, 1H), 2.88 (dd, J = 6.15 Hz, 14.12 Hz, 1H), 1.92 - 1.70 (m, 1H), 1.17 (t, J = 7.06 Hz, 3H), 0.89 (d, J = 6.69 Hz, 3H), 0.82 (d, J = 6.69 Hz, 3H).

29b :  $[\alpha]_D^{25} = -29.48^\circ$  (c = 1.0; CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  8.44 (d, J = 8.29 Hz, 1H), 8.19 (s, 1H), 7.90 - 7.68 (m, 3H), 7.11 (d, J = 8.39 Hz, 2H), 6.82 (d, J = 8.39 Hz, 2H), 4.63 (t, J = 5.09 Hz, 2H), 4.38 (t, J = 5.09 Hz, 2H), 3.95 - 3.89 (m, 1H), 3.70 - 3.35 (m, 5H), 3.05 (dd, J = 3.65 Hz, 14.35 Hz, 1H), 2.82 (dd, J = 7.15 Hz, 14.12 Hz, 1H), 1.85 - 1.70 (m, 1H), 1.17 (t, J = 6.97 Hz, 3H), 0.91 - 0.70 (m, 6H).

### Example 30

(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid



A solution of [(2S), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (0.71 g, 1.42 mmol) (obtained from example 28b) in a mixture of 1 M sulfuric acid (18.4 mL) and dioxane / water (1 : 1.64 mL) was heated at 90 °C for 48 h and then the pH of the

mixture was adjusted to pH 4 by addition of aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the organic extracts were washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to give an oil (0.33 g, 63.4 %). The oil was crystallised by triturating with diethyl ether to give white solid, which contained  
5 two polymorphs, with DSC endotherms at 104 °C and 121 °C.

**Alternate Method :** The title compound was prepared as a solid (0.73 g, 90 %) from [(2S), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]-N-(2-hydroxy-1-isopropylethyl)propanamide (0.1 g, 0.214 mmol) (obtained from example 29b) as described above.

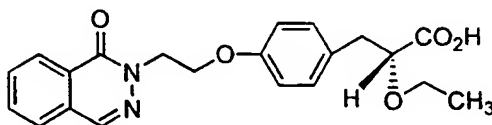
10  $[\alpha]_D^{25} = -12.0$  (c = 1.0, CHCl<sub>3</sub>) 98 % e.e. (by HPLC);

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) :  $\delta$  8.46 (d, J = 8.90 Hz, 1H), 8.19 (s, 1H), 7.82 - 7.72 (m, 3H), 7.13 (d, J = 8.30 Hz, 2H), 6.87 (d, J = 8.30 Hz, 2H), 4.64 (t, J = 5.82 Hz, 2H), 4.40 (t, J = 5.82 Hz, 2H), 4.05 - 3.90 (m, 1H), 3.55 - 3.39 (m, 2H), 3.02 (dd, J = 4.15 and 14.11 Hz, 1H), 2.90 (dd, J = 7.47 and 14.11 Hz, 1H), 1.19 (t, J = 6.96 Hz, 3H).

15

### Example 31

(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid  
20 acid



A solution of [(2R), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)phenyl]-N-(2-hydroxy-1-isopropylethyl)propanamide (0.1 g, 0.214 mmol) (obtained from example 29a) in a mixture of 1M H<sub>2</sub>SO<sub>4</sub> (2.85 mL) and dioxane/water (1:1.5 mL)  
25 was heated at 90 °C for 24 h. The pH of the mixture was adjusted to 4 by addition of aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the organic extracts were washed with water, brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to give an oil (0.73 g, 90 %). The oil was crystallised by triturating with  
30 diethyl ether to give white solid.

**Alternate method :** The title compound can also be prepared (0.3 g, 64 %) from [(2R), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (0.7 g, 1.4 mmol) (obtained from example 28a) using a similar procedure as described above.

5  $[\alpha]_D^{25} = 11.4^\circ$  (c = 1.0, CHCl<sub>3</sub>) 97 % e.e. (by HPLC);

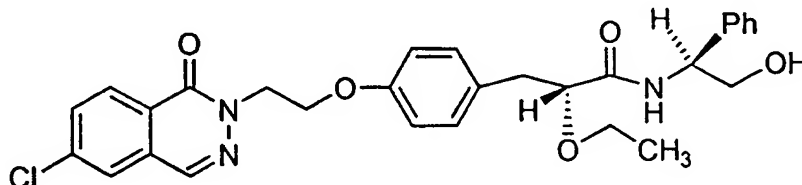
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) :  $\delta$  8.44 (d, J = 8.9 Hz, 1H), 8.19 (s, 1H), 7.90 - 7.60 (m, 3H), 7.12 (d, J = 8.30 Hz, 2H), 6.84 (d, J = 8.30 Hz, 2H), 4.64 (t, J = 5.72 Hz, 2H), 4.40 (t, J = 5.72 Hz, 2H), 4.05 - 3.90 (m, 1H), 3.60 - 3.38 (m, 2H), 3.02 (dd, J = 4.15 Hz, J = 14.11 Hz, 1H), 2.90 (dd, J = 7.47 Hz, J = 14.11 Hz, 1H), 1.15 (t, J = 6.92 Hz, 3H).

10

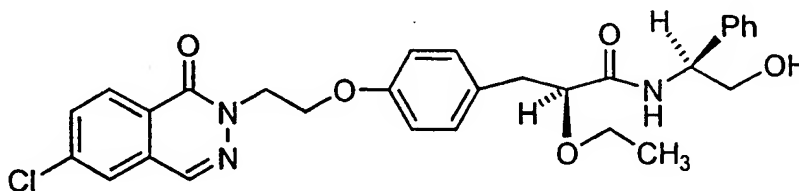
**Example 32 :**

**[2R, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyloxy)]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (32a)**

15



**[2S, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyloxy)]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (32b)**



20 The title compounds were obtained as oil (0.06 g of 32a and 0.06 g of 32b) from (±) 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyloxy)]phenyl]propanoic acid (0.1 g, 0.24 mmol) obtained from example 24 and S(+) phenyl glycinol (0.037 g, 0.264 mmol) by a similar procedure to that described in example 28.

32a :  $[\alpha]_D^{25} = 19.0$  (C=1, CHCl<sub>3</sub>), 98 % e.e. (by HPLC)

25 <sup>1</sup>H NMR : (CDCl<sub>3</sub>, 200 MHz) :  $\delta$  8.36 (d, J = 12.7 Hz, 1H), 8.12 (d, J = 8.50 Hz, 1H), 7.80 - 7.60 (m, 2H), 7.40 - 7.25 (m, 5H), 7.15 (d, J = 7.98 Hz, 2H), 6.84 (d, J = 7.98 Hz,

2H), 5.00 – 4.90 (m, 1H), 4.61 (t,  $J = 5.49$  Hz, 2H), 4.41 (t,  $J = 5.49$  Hz, 2H), 4.09 – 3.94 (m, 1H), 3.70 – 3.40 (m, 4H), 3.04 (dd,  $J = 3.74$  Hz, 16.5 Hz, 1H), 2.92 (dd,  $J = 5.82$  and 16.5 Hz, 1H), 1.12 (t,  $J = 6.83$  Hz, 3H).

32b :  $[\alpha]^{25}_D = 16.2$  (C=1,  $\text{CHCl}_3$ ), 97 % e.e (by HPLC)

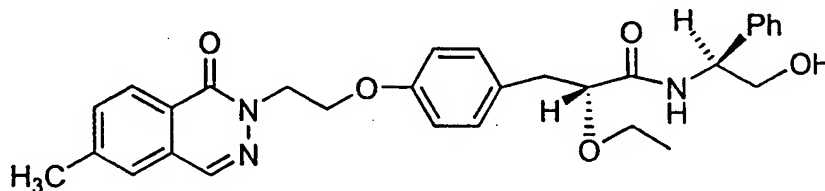
5  $^1\text{H NMR}$  : ( $\text{CDCl}_3$ , 200 MHz) : 8.36 (d,  $J = 12.7$  Hz, 1H), 8.14 (d,  $J = 8.50$  Hz, 1H), 7.87 – 7.56 (m, 2H), 7.42 – 7.27 (m, 5H), 7.17 (d,  $J = 8.03$  Hz, 2H), 6.84 (d,  $J = 8.03$  Hz, 2H), 5.0 – 4.90 (m, 1H), 4.64 (t,  $J = 5.48$  Hz, 2H), 4.40 (t,  $J = 5.48$  Hz, 2H), 4.09 – 3.92 (m, 1H), 3.70 – 3.42 (m, 4H), 3.07 (dd,  $J = 3.74$  and 16.5 Hz, 1H), 2.96 (dd,  $J = 5.82$  and 16.5 Hz, 1H), 1.16 (t,  $J = 6.83$  Hz, 3H).

10

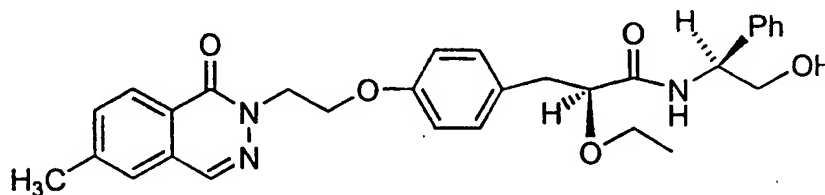
### Example 33 :

[2R, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (33a)

15



[2S, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (33b)



20 The title compounds were obtained as oil (0.12 g of 33a and 0.105 g of 33b) from ( $\pm$ ) 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]propanoic acid (0.205 g, 0.517 mmol) obtained from example 26 and S(+) phenyl glycinol (0.08 g, 0.569 mmol) by a similar procedure to that described in example 28.

33a :  $[\alpha]^{25}_D = 19.8$  (C=1,  $\text{CHCl}_3$ ), 97 % e.e (by HPLC)

25  $^1\text{H NMR}$  : ( $\text{CDCl}_3$ , 200 MHz) :  $\delta$  8.30 (d,  $J = 8.21$  Hz, 1H), 8.12 (s, 1H), 7.58 (d,  $J = 9.12$  Hz, 1H), 7.47 (s, 1H), 7.39 – 7.12 (m, 7H), 6.86 (d,  $J = 10.43$  Hz, 2H), 5.00 - 4.90

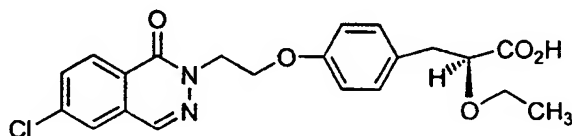
(m, 1H), 4.61 (t, J = 6.14 Hz, 2H), 4.42 (t, J = 6.14 Hz, 2H), 4.00 – 3.94 (m, 1H), 3.80 – 3.40 (m, 4H), 3.11 (dd, J = 3.82 and 14.11 Hz, 1H), 2.93 (dd, J = 5.82 and 14.1 Hz, 1H), 2.54 (s, 3H), 1.14 (t, J = 7.06 Hz, 3H).

33b :  $[\alpha]_D^{25} = 16.0$  (C=1, CHCl<sub>3</sub>), 97 % e.e (by HPLC)

5 <sup>1</sup>H NMR : (CDCl<sub>3</sub>, 200 MHz) : δ 8.27 (d, J = 7.79 Hz, 1H), 8.12 (s, 1H), 7.50 (s, 1H), 7.58 (d, J = 9.12 Hz, 1H), 7.38 – 7.12 (m, 7H), 6.89 (d, J = 10.43 Hz, 2H), 5.10 – 4.90 (m, 1H), 4.70 (t, J = 6.14 Hz, 2H), 4.49 (t, J = 6.14 Hz, 2H), 3.99 – 3.94 (m, 1H), 3.84 – 3.49 (m, 4H), 3.09 (m, 4H), 3.09 (dd, J = 3.82 and 14.1 Hz, 1H), 2.93 (dd, J = 6.34 and 14.1 Hz, 1H), 2.93 (dd, J = 6.34 and 14.1 Hz, 1H), 2.54 (s, 3H), 1.16 (t, J = 7.06 Hz, 3H).

#### Example 34 :

(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]propanoic acid



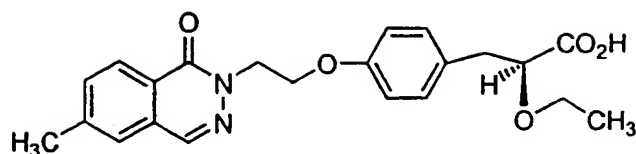
15 The title compound was prepared as a white solid (0.13 g, 76.5 %) from [(2S), N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (0.22 g, 0.41 mmol) obtained from example 32b by a similar procedure to that described in example 30, mp : 135 – 140 °C.

20  $[\alpha]_D^{25} = 12.6$  (C=1, CHCl<sub>3</sub>), 96 % e.e (by HPLC)

<sup>1</sup>H NMR : (CDCl<sub>3</sub>, 200 MHz) : δ 8.36 (d, J = 8.30 Hz, 1H), 8.10 (s, 1H), 7.69 (d, J = 8.30 Hz, 1H), 7.25 (s, 1H), 7.10 (d, J = 8.63 Hz, 2H), 6.82 (d, J = 8.63 Hz, 2H), 4.61 (t, J = 5.81 Hz, 2H), 4.38 (t, J = 5.81 Hz, 2H), 4.05 – 3.90 (m, 1H), 3.60 – 3.35 (m, 2H), 3.02 (dd, J = 4.15 and 14.2 Hz, 1H), 2.85 (dd, J = 7.06 and 14.2 Hz, 1H), 1.15 (t, J = 6.97 Hz, 3H).

#### Example 35 :

(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]propanoic acid.

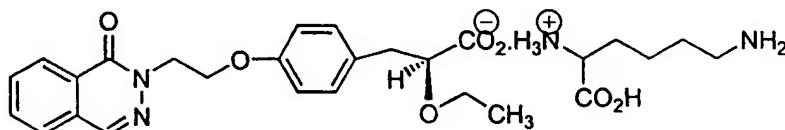


The title compound was prepared as a white solid (45 mg, 56.2 %) from [(2S), N(1S)]-2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (0.105 g, 0.203 mmol) obtained from example 33b  
 5 by a similar procedure to that described in example 30, mp : 140 – 142 °C.  
 $[\alpha]^{25}_D = 12.2$  (C=1,  $\text{CHCl}_3$ ), 97 % e.e (by HPLC)

$^1\text{H}$  NMR : ( $\text{CDCl}_3$ , 200 MHz) :  $\delta$  8.32 (d, J = 8.31 Hz, 1H), 8.12 (s, 1H), 7.59 (d, J = 8.31 Hz, 1H), 8.12 (s, 1H), 7.59 (d, J = 8.31 Hz, 1H), 7.48 (s, 1H), 7.12 (d, J = 8.43 Hz, 2H), 6.85 (d, J = 8.43 Hz, 2H), 4.62 (t, J = 5.82 Hz, 2H), 4.06 – 3.90 (m, 1H), 3.60- 3.35  
 10 (m, 2H), 3.07 (dd, J = 4.25 and 14.2 Hz, 1H), 2.92 (dd, J = 6.87 and 14.2 Hz, 1H), 2.54 (s, 3H), 1.16 (t, J = 7.01 Hz, 3H).

#### Example 36 :

(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic  
 15 acid lysine salt



To a stirred solution of (-)-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid (200 g, 0.52 mmol) obtained from example 30 in methanol (10 mL) was added L-lysine (77.62 mg, 0.47 mmol) and stirred the reaction mixture at 25 °C  
 20 for 24 h. The methanol was evaporated under reduced pressure and the residue was washed with 20 mL of ethyl acetate and then with 20 mL of dry ethyl ether dried under vacuum for 4 h to obtain (245 mg, 99 %) of the lysine salt, mp : 164 °C.

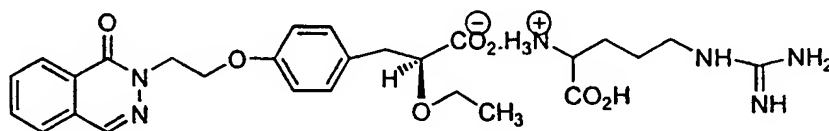
$[\alpha]^{25}_D = 10.5$  (C= 0.5,  $\text{CHCl}_3$ ), 97 % e.e (by HPLC)

$^1\text{H}$  NMR : ( $\text{CDCl}_3$ , 200 MHz) :  $\delta$  8.36 (d, J = 5.99 Hz, 2H), 7.91 – 7.80 (m, 3H), 7.14 (d, J = 8.63 Hz, 2H), 6.79 (d, J = 8.63 Hz, 2H), 4.60 (t, J = 5.49 Hz, 2H), 4.40 (t, J = 5.49 Hz, 2H), 3.77 – 3.71 (m, 1H), 3.60- 3.15 (m, 3H), 2.91 – 2.84 (m, 2H), 2.85 (dd, J = 3.72  
 25

and 14.1 Hz, 1H), 2.75 (dd,  $J = 7.72$  and  $14.1$  Hz, 1H), 1.90 – 1.40 (m, 6H), 1.07 (t,  $J = 7.00$  Hz, 3H).

**Example 37 :**

- 5    (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid arginine salt



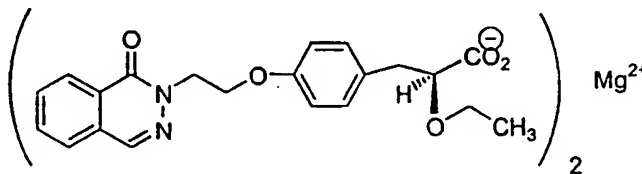
The title compound was obtained as a white solid (260 mg, 99 %) from (-) 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid (200 mg, 0.52 mmol) obtained from example 30 and L-arginine (82.25 mg, 0.472 mmol) by a similar procedure to that described in example 36, mp : 71 °C.

$[\alpha]_D^{25} = 8.0$  ( $C = 0.5$ ,  $\text{CHCl}_3$ ), 97 % e.e (by HPLC)

$^1\text{H}$  NMR : ( $\text{CDCl}_3$ , 200 MHz) :  $\delta$  8.38 (d,  $J = 5.40$  Hz, 2H), 7.94 – 7.87 (m, 3H), 7.15 (d,  $J = 8.58$  Hz, 2H), 6.81 (d,  $J = 8.58$  Hz, 2H), 4.63 (t,  $J = 5.81$  Hz, 2H), 4.43 (t,  $J = 5.81$  Hz, 2H), 3.80 – 3.75 (m, 1H), 3.65– 3.51 (m, 2H), 3.36 – 3.18 (m, 3H), 2.92 (dd,  $J = 4.15$  and 13.8 Hz, 1H), 1.92 – 1.72 (m, 4H), 1.11 (t,  $J = 6.92$  Hz, 3H).

**Example 38 :**

- 20    (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid magnesium salt



The title compound was obtained as a white solid (175 mg, 86 %) from (-) 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid (208.6 mg, 0.546 mmol) and  $\text{Mg}(\text{OH})_2$  (15 mg, 0.26 mmol) in methanol (10 mL) by a similar procedure to that described in example 36, mp : 244 - 246 °C.

$^1\text{H}$  NMR : ( $\text{d}^4\text{-CD}_3\text{OD}$ , 200 MHz) :  $\delta$  8.35 – 8.31 (m, 2H), 7.90 – 7.81 (m, 3H), 7.13 (d,  $J = 8.39$  Hz, 2H), 4.59 (t,  $J = 5.40$  Hz, 2H), 4.38 (t,  $J = 5.40$  Hz, 2H), 3.85 – 3.70 (m,

1H), 3.65- 3.18 (m, 2H), 2.90 (dd, J = 10.9 and 13.3 Hz, 1H), 2.77 (dd, J = 4.87 and 13.3 Hz, 1H), 1.06 (t, J = 6.90 Hz, 3H).

As used in the examples brine means sodium chloride salt solution.

5

The compounds of the present invention lowered random blood sugar level, triglyceride, total cholesterol, LDL, VLDL, free fatty acids and increased HDL. This was demonstrated by *in vitro* as well as *in vivo* animal experiments.

10 Demonstration of Efficacy of Compounds :

A) In vitro :

a) Determination of hPPAR $\alpha$  activity :

Ligand binding domain of hPPAR $\alpha$  was fused to DNA binding domain of Yeast  
15 transcription factor GAL4 in eucaryotic expression vector. Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at different concentrations after 42 hrs of transfection and incubated overnight. Luciferase activity as a function of compound binding/activation  
20 capacity of PPAR $\alpha$  was measured using Packard Luclite kit (Packard, USA) in Top Count (Ivan Sadowski, Brendan Bell, Peter Broag and Melvyn Hollis. Gene. 1992. 118 : 137 -141; Superfect Transfection Reagent Handbook. February, 1997. Qiagen, Germany).

25 b) Determination of hPPAR $\gamma$  activity :

Ligand binding domain of hPPAR $\gamma$ 1 was fused to DNA binding domain of Yeast  
transcription factor GAL4 in eucaryotic expression vector. Using lipofectamine (Gibco  
BRL, USA) as transfecting reagent HEK-293 cells were transfected with this plasmid  
and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific  
30 promoter. Compound was added at 1  $\mu$ M concentration after 48 hrs of transfection and incubated overnight. Luciferase activity as a function of drug binding/activation capacity



of PPAR $\gamma$ 1 was measured using Packard Luclite kit (Packard, USA) in Packard Top Count (Ivan Sadowski, Brendan Bell, Peter Broag and Melvyn Hollis. Gene. 1992. 118 : 137 –141; Guide to Eukaryotic Transfections with Cationic Lipid Reagents. Life Technologies, GIBCO BRL, USA).

5

Example No	Concentration	PPAR $\alpha$	Concentration	PPAR $\gamma$
Example 12	50 $\mu$ M	11.39	1 $\mu$ M	9.91
Example 15	50 $\mu$ M	0.9	1 $\mu$ M	1.05
Example 16	50 $\mu$ M	4.7	1 $\mu$ M	11.83
Example 22	50 $\mu$ M	3.7	1 $\mu$ M	17.69
Example 23	50 $\mu$ M	3.79	1 $\mu$ M	16.13

- c) **Determination of HMG CoA reductase inhibition activity** : Liver microsome bound reductase was prepared from 2% cholestyramine fed rats at mid-dark cycle. Spectrophotometric assays were carried out in 100 mM KH<sub>2</sub>PO<sub>4</sub>, 4 mM DTT, 0.2 mM NADPH, 0.3 mM HMG CoA and 125  $\mu$ g of liver microsomal enzyme. Total reaction mixture volume was kept as 1 ml. Reaction was started by addition of HMG CoA. Reaction mixture was incubated at 37 °C for 30 min and decrease in absorbance at 340 nm was recorded. Reaction mixture without substrate was used as blank (Goldstein, J. L and Brown, M. S. Progress in understanding the LDL receptor and HMG CoA reductase, two membrane proteins that regulate the plasma cholesterol. J. Lipid Res. 1984, 25: 1450 – 1461). The test compounds inhibited the HMG CoA reductase enzyme.

**B) In vivo :**

**Efficacy in genetic models :**

- Mutation in colonies of laboratory animals and different sensitivities to dietary regimens have made the development of animal models with non-insulin dependent diabetes and hyperlipidemia associated with obesity and insulin resistance possible. Genetic models such as db/db and ob/ob (Diabetes, (1982) 31(1) : 1- 6) mice and zucker fa/fa rats have been developed by the various laboratories for understanding the pathophysiology of disease and testing the efficacy of new antidiabetic compounds

(Diabetes, (1983) 32: 830-838 ; Annu. Rep. Sankyo Res. Lab. (1994). 46 : 1-57). The homozygous animals, C57 BL/KsJ-db/db mice developed by Jackson Laboratory, US, are obese, hyperglycemic, hyperinsulinemic and insulin resistant (J. Clin. Invest., (1990) 85 : 962-967), whereas heterozygous animals are lean and normoglycemic. In the db/db model, a mouse progressively develops insulinopenia with age, a feature commonly observed in late stages of human type II diabetes when blood sugar levels are insufficiently controlled. The state of pancreas and its course vary according to the models. Since this model resembles that of type II diabetes mellitus, the compounds of the present invention were tested for blood sugar and triglycerides lowering activities.

Male C57BL/KsJ-db/db mice of 8 to 14 weeks age, having body weight range of 35 to 60 grams, bred at Dr. Reddy's Research Foundation (DRF) animal house, were used in the experiment. The mice were provided with standard feed (National Institute of Nutrition (NIN), Hyderabad, India) and acidified water, ad libitum. The animals having more than 350 mg / dl blood sugar were used for testing. The number of animals in each group was 4.

Test compounds were suspended on 0.25 % carboxymethyl cellulose and administered to test group at a dose of 0.1 mg to 30 mg / kg through oral gavage daily for 6 days. The control group received vehicle (dose 10 ml / kg). On 6th day the blood samples were collected one hour after administration of test compounds / vehicle for assessing the biological activity.

The random blood sugar and triglyceride levels were measured by collecting blood (100 µl) through orbital sinus, using heparinised capillary in tubes containing EDTA which was centrifuged to obtain plasma. The plasma glucose and triglyceride levels were measured spectrometrically, by glucose oxidase and glycerol-3-PO<sub>4</sub> oxidase/oxidase enzyme (Dr. Reddy's Lab. Diagnostic Division Kits, Hyderabad, India) methods respectively.

The blood sugar and triglycerides lowering activities of the test compound was calculated according to the formula.

No adverse effects were observed for any of the mentioned compounds of invention in the above test.

Compound	Dose (mg / kg)	Reduction in Blood Glucose Level (%)	Triglyceride Lowering (%)
Example 12	3 mg	66	66
Example 16	3 mg	55	33

The ob/ob mice were obtained at 5 weeks of age from Bomholtgard, Demark and were used at 8 weeks of age. Zucker fa/fa fatty rats were obtained from IffaCredo, France at 10 weeks of age and were used at 13 weeks of age. The animals were maintained under 12 hour light and dark cycle at  $25 \pm 1$  °C. Animals were given standard laboratory chow (NIN, Hyderabad, India) and water, *ad libitum* (Fujiwara, T., Yoshioka, S., Yoshioka, T., Ushiyama, I. and Horikoshi, H. Characterization of new oral antidiabetic agent CS-045. Studies in KK and ob/ob mice and Zucker fatty rats. Diabetes. 1988. 37 : 1549 – 1558).

The test compounds were administered at 0.1 to 30 mg/kg/day dose for 9 days. The control animals received the vehicle (0.25 % carboxymethylcellulose, dose 10 ml/kg) through oral gavage.

The blood samples were collected in fed state 1 hour after drug administration on 0 and 9 day of treatment. The blood was collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for triglyceride, glucose, free fatty acid, total cholesterol and insulin estimations. Measurement of plasma triglyceride, glucose, total cholesterol were done using commercial kits (Dr. Reddy's Laboratory, Diagnostic Division, India). The plasma free fatty acid was measured using a commercial kit form Boehringer Mannheim, Germany. The plasma insulin was measured using a RIA kit (BARC, India). The reduction of various parameters examined are calculated according to the formula shown below.

In ob/ob mice oral glucose tolerance test was performed after 9 days treatment. Mice were fasted for 5 hrs and challenged with 3 gm/kg of glucose orally. The blood samples were collected at 0, 15, 30, 60 and 120 min for estimation of plasma glucose levels.

The experimental results from the db/db mice, ob/ob mice, Zucker fa/fa rats suggest that the novel compounds of the present invention also possess therapeutic utility as a prophylactic or regular treatment for diabetes, obesity, cardiovascular disorders such as hypertension, hyperlipidaemia and other diseases; as it is known from the literature that such diseases are interrelated to each other.

Blood glucose level and triglycerides are also lowered at doses greater than 10 mg/kg. Normally, the quantum of reduction is dose dependent and plateaus at certain dose.

**b) Cholesterol lowering activity in hypercholesterolemic rat models :**

Male Sprague Dawley rats (NIN stock) were bred in DRF animal house. Animals were maintained under 12 hour light and dark cycle at  $25 \pm 1^{\circ}\text{C}$ . Rats of 180 - 200 gram body weight range were used for the experiment. Animals were made hypercholesterolemic by feeding 2% cholesterol and 1% sodium cholate mixed with standard laboratory chow [National Institute of Nutrition (NIN), Hyderabad, India] for 6 days. Throughout the experimental period the animals were maintained on the same diet (Petit, D., Bonnefis, M. T., Rey, C and Infante, R. Effects of ciprofibrate on liver lipids and lipoprotein synthesis in normo- and hyperlipidemic rats. Atherosclerosis. 1988. 74 : 215 – 225).

The test compounds were administered orally at a dose 0.1 to 30 mg/kg/day for 3 days. Control group was treated with vehicle alone (0.25 % Carboxymethylcellulose; dose 10 ml/kg).

The blood samples were collected in fed state 1 hour after drug administration on 0 and 3 day of compound treatment. The blood was collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for total cholesterol, HDL and triglyceride estimations. Measurement of plasma triglyceride, total cholesterol and HDL were done using commercial kits (Dr. Reddy's Laboratory, Diagnostic Division, India). LDL and VLDL cholesterol were calculated from the data obtained for total cholesterol, HDL and triglyceride. The reduction of various parameters examined are calculated according to the formula.

**c) Plasma triglyceride and total cholesterol lowering activity in Swiss albino mice and Guinea pigs :**

Male Swiss albino mice (SAM) and male Guinea pigs were obtained from NIN and housed in DRF animal house. All these animals were maintained under 12 hour light and dark cycle at  $25 \pm 1^{\circ}\text{C}$ . Animals were given standard laboratory chow (NTN, Hyderabad, India) and water, *ad libitum*. SAM of 20 - 25 g body weight range and Guinea pigs of 500 - 700 g body weight range were used (Oliver, P., Plancke, M. O., Marzin, D., Clavey, V., Sauzieres, J and Fruchart, J. C. Effects of fenofibrate, gemfibrozil and nicotinic acid on plasma lipoprotein levels in normal and hyperlipidemic mice. Atherosclerosis. 1988. 70 : 107 - 114).

The test compounds were administered orally to Swiss albino mice at 0.3 to 30 mg/kg/day dose for 6 days. Control mice were treated with vehicle (0.25% Carboxymethylcellulose; dose 10 ml/kg). The test compounds were administered orally to Guinea pigs at 0.3 to 30 mg/kg/day dose for 6 days. Control animals were treated with vehicle (0.25% Carboxymethylcellulose; dose 5 ml/kg).

The blood samples were collected in fed state 1 hour after drug administration on 0 and 6 day of treatment. The blood was collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for triglyceride and total cholesterol (Wieland, O. Methods of Enzymatic analysis. Bergermeyer, H. O., Ed., 1963. 211 - 214; Trinder, P. Ann. Clin. Biochem. 1969. 6 : 24 - 27). Measurement of plasma triglyceride, total cholesterol and HDL were done using commercial kits (Dr. Reddy's Diagnostic Division, Hyderabad, India).

Compound	Dose (mg / kg)	Triglyceride Lowering (%)
Example 22	3 mg	60
Example 27	10 mg	69
Example 38	1 mg	46

*Formulae for calculation :*

- Percent reduction in Blood sugar / triglycerides / total cholesterol were calculated according to the formula :

$$\text{Percent reduction (\%)} = \left[ 1 - \frac{\text{TT / OT}}{\text{TC / OC}} \right] \times 100$$

OC = Zero day control group value

OT = Zero day treated group value

TC = Test day control group value

5 TT = Test day treated group value

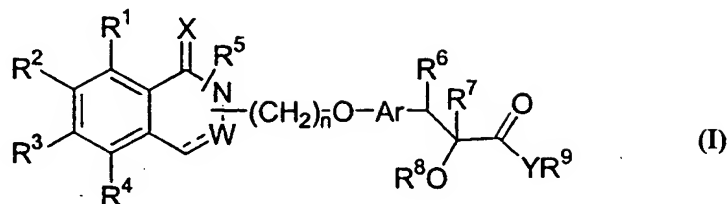
2. LDL and VLDL cholesterol levels were calculated according to the formula :

$$\text{LDL cholesterol in mg/dl} = \left[ \text{Total cholesterol} - \text{HDL cholesterol} - \frac{\text{Triglyceride}}{5} \right] \text{ mg/dl}$$

$$\text{VLDL cholesterol in mg/dl} = [\text{Total cholesterol} - \text{HDL cholesterol} - \text{LDL cholesterol}] \text{ mg/dl}$$

## Claims :

1. A compound of formula (I)



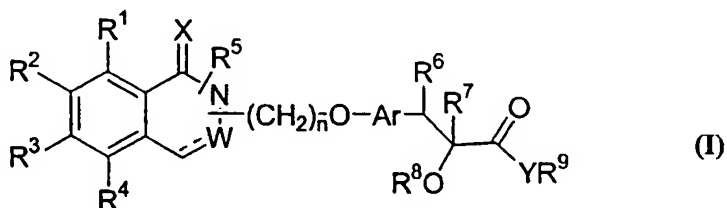
- its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, or its pharmaceutically acceptable solvates, wherein X represents O or S; the groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy carbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxy carbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of R<sup>1</sup> to R<sup>4</sup> together with the adjacent carbon atoms to which they are attached may also form a 5-6 membered cyclic structure containing carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains an oxo group; "----" represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that when W represents nitrogen atom, "----" represents a bond or no bond and when W represents an oxygen atom "----" represents no bond; R<sup>5</sup> when present on carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy carbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxy carbonylamino, aralkoxycarbonylamino,

alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives;  $R^5$  when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group;  $R^6$  represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group  $R^7$ ;  $R^7$  represents hydrogen, hydroxy, alkoxy, halogen, acyl, lower alkyl group or unsubstituted or substituted aralkyl or  $R^7$  forms a bond together with  $R^6$ ;  $R^8$  represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl group;  $R^9$  represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; Y represents an oxygen or  $NR^{10}$ , where  $R^{10}$  represents hydrogen, alkyl, aryl, hydroxyalkyl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; or  $R^9$  and  $R^{10}$  together form a 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen and the linker group represented by  $-(CH_2)_n-O-$  is attached either through nitrogen atom or through carbon atom, where n is an integer ranging from 1-4.

2. A compound according to claim 1, wherein the substituents on the groups represented by  $R^1 - R^4$  and the groups  $R^5$  when attached to carbon atom are selected from halogen, hydroxy, or nitro or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives.



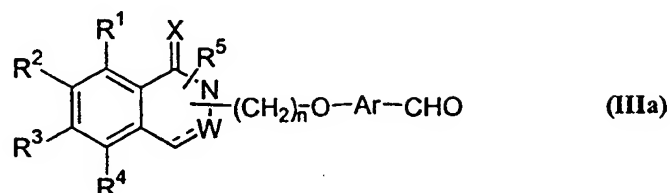
3. A compound according to claim 1, wherein the substituents on the group  $R^5$  when attached to nitrogen are selected from halogen such as fluorine, chlorine; hydroxy, acyl, acyloxy or amino groups.
- 5 4. A compound according to claim 1, wherein Ar represents unsubstituted or substituted divalent phenylene, naphthylene, pyridyl, quinolinyl, benzopyranyl, benzofuryl, indolyl, indolinyl, azaindolyl, azaindolyl, indenyl, dihydrobenzofuryl, dihydrobenzopyranyl, pyrazolyl, benzoxazolyl or benzothiazolyl group.
- 10 5. A compound according to claim 1, wherein the substituents on the group represented by  $R^8$  are selected from halogen, hydroxy, formyl or nitro or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, 15 alkoxylalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives .
6. A process for the preparation of compound of formula (I)



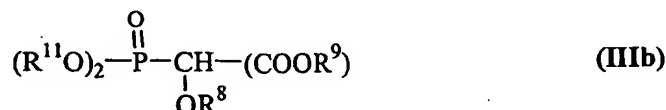
- 20 its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts or its pharmaceutically acceptable solvates, wherein X represents O or S; the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, 25 heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxylalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino,

aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of  $R^1$  to  $R^4$  together with the adjacent carbon atoms to which they are attached may also form a 5-6 membered cyclic structure containing carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains an oxo group; "----" represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that when W represents nitrogen atom, "----" represents a bond or no bond and when W represents an oxygen atom "----" represents no bond;  $R^5$  when present on carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkyamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives;  $R^5$  when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkyamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group;  $R^6$  together with  $R^7$  represent a bond;  $R^8$  represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl group;  $R^9$  represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; Y represents an oxygen and the linker group represented by  $-(CH_2)_n-O-$  is attached either through nitrogen atom or through carbon atom, where n is an integer ranging from 1-4, which comprises :

a) reacting a compound of formula (IIIa)

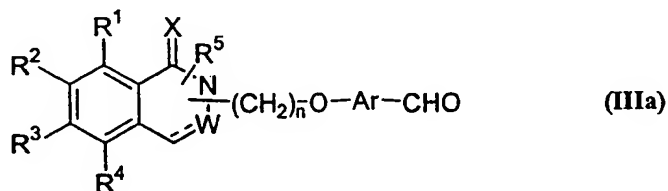


where all symbols are as defined above with a compound of formula (IIIb)



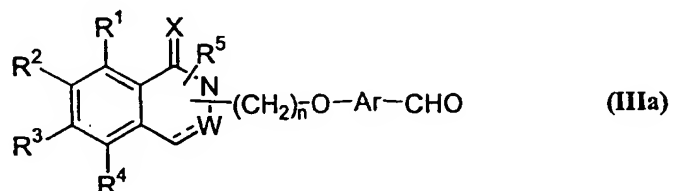
5 where R<sup>8</sup> and R<sup>9</sup> are as defined above excluding hydrogen and R<sup>11</sup> represents (C<sub>1</sub>-C<sub>6</sub>)alkyl, to yield compound of general formula (I) defined above;

b) reacting a compound of formula (IIIa)

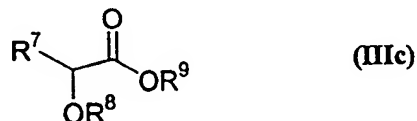


where all symbols are as defined earlier with Wittig reagents;

10 c) reacting a compound of formula (IIIa)



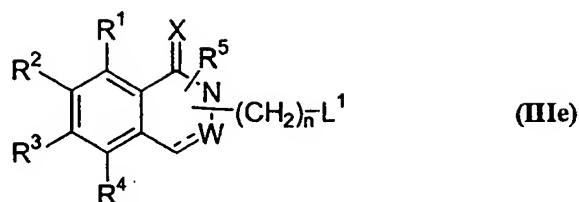
where all other symbols are as defined above with a compound of formula (IIIc)



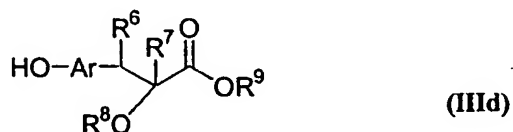
where R<sup>7</sup> is hydrogen, R<sup>8</sup> and R<sup>9</sup> are as defined above to yield a compound of formula

15 (I) as defined above;

d) reacting a compound of formula (IIIe)

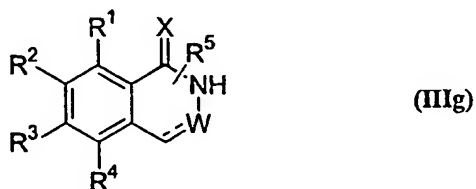


where all symbols are as defined earlier and  $L^1$  represents a leaving group, with compound of formula (IIIId)

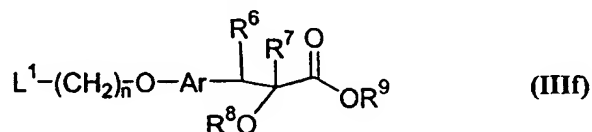


- 5 where  $R^6$  and  $R^7$  together represent a bond and  $R^8$ ,  $R^9$  and Ar are as defined earlier to produce a compound of the formula (I) where all symbols are as defined above;

e) reacting a compound of formula (IIIg)



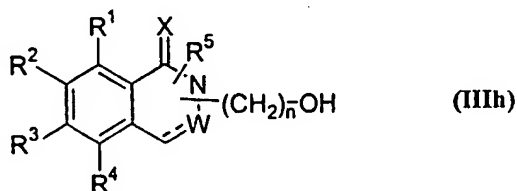
where all symbols are as defined above with a compound of formula (IIIf)



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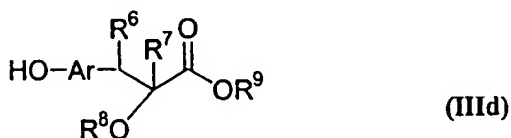
where  $R^6$  and  $R^7$  together represent a bond and all symbols are as defined above and  $L^1$  is a leaving group to produce a compound of general formula (I) defined above, where the linker group  $-(CH_2)_n-O-$  is attached to nitrogen atom;

f) reacting a compound of formula (IIIh)



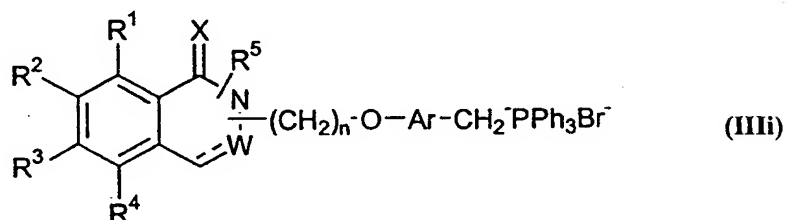
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where all symbols are as defined above with a compound of formula (IIIId)

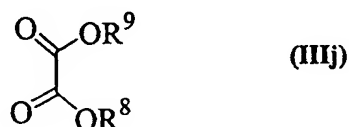


where R<sup>6</sup> and R<sup>7</sup> together represent a bond and R<sup>8</sup>, R<sup>9</sup> and Ar are as defined above to produce a compound of formula (I) as defined above;

g) reacting a compound of formula (IIIi)



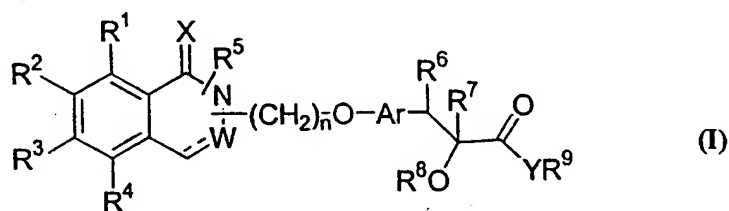
5 where all symbols are as defined above with a compound of formula (IIIj)



where  $R^8 = R^9$  and are as defined above excluding hydrogen to produce a compound of the formula (I) and optionally;

h) converting the compounds of formula (I) obtained in any of the processes described above into pharmaceutically acceptable salts or pharmaceutically acceptable solvates.

7. A process for the preparation of compound of formula (I)

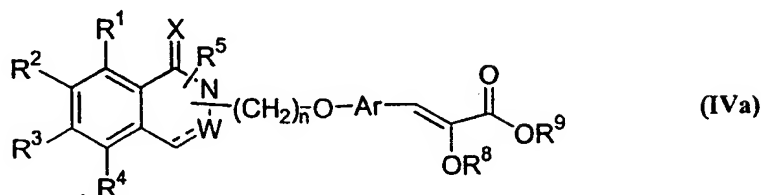


its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts or its pharmaceutically acceptable solvates, wherein X represents O or S; the groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkyamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino,

aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of  $R^1$  to  $R^4$  together with the adjacent carbon atoms to which they are attached may also form a 5-6 membered cyclic structure containing carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains an oxo group; "----" represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that when W represents nitrogen atom, "----" represents a bond or no bond and when W represents an oxygen atom "----" represents no bond;  $R^5$  when present on carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy carbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxy carbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives;  $R^5$  when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxy carbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group;  $R^6$  represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or substituted aralkyl group;  $R^7$  represents hydrogen, hydroxy, alkoxy, halogen, acyl, lower alkyl group or unsubstituted or substituted aralkyl;  $R^8$  represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl group;  $R^9$  represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; Y represents an oxygen and the linker group represented by  $-(CH_2)_n-O-$  is

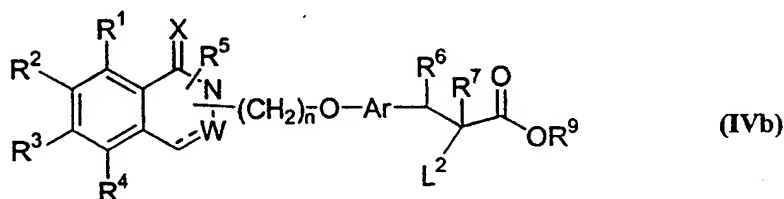
attached either through nitrogen atom or through carbon atom, where  $n$  is an integer ranging from 1-4, which comprises :

a) reducing a compound of formula (IVa)



5 which represents a compound of formula (I) where  $R^6$  and  $R^7$  together represent a bond and  $Y$  represent oxygen atom and all other symbols are as defined above, to yield a compound of the general formula (I) where  $R^6$  and  $R^7$  each represent hydrogen atom and all symbols are as defined above;

b) reacting a compound of formula (IVb)



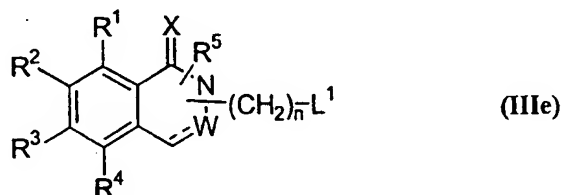
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where all symbols are as defined above,  $R^9$  is as defined above excluding hydrogen and  $L^2$  is a leaving group with an alcohol of general formula (IVc),

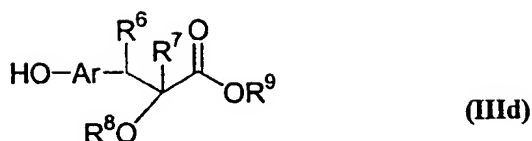


where  $R^8$  represents unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxy carbonyl, aryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl to produce a compound of the formula (I) where all symbols are as defined above;

c) reacting a compound of formula (IIIe)

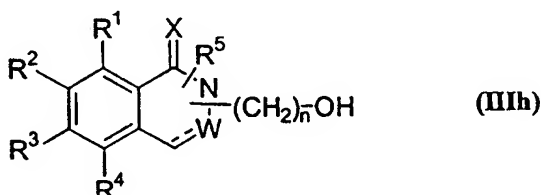


20 where  $L^1$  is a leaving group and all other symbols are as defined above with a compound of formula (IIIId)



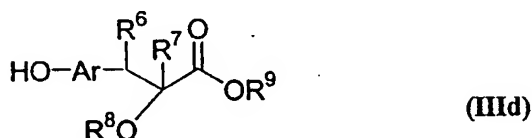
where all symbols are as defined above to produce a compound of the formula (I) where all symbols are as defined above;

d) reacting a compound of formula (IIIh)



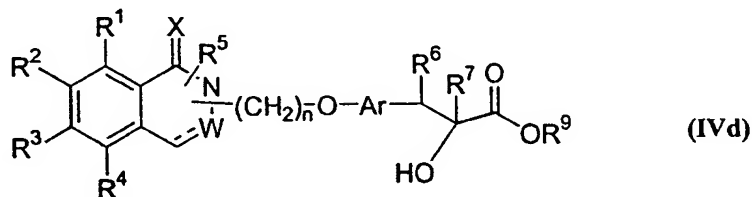
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where all symbols are as defined above with a compound of formula (IIIId)



where all symbols are as defined above to produce a compound of formula (I) where all symbols are as defined above;

10 e) reacting a compound of formula (IVd)



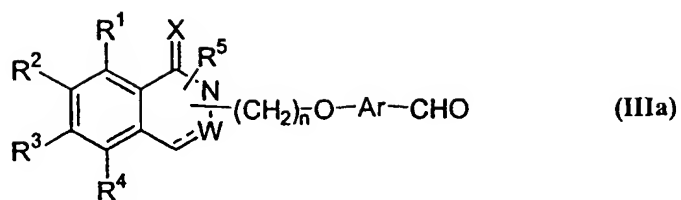
which represents a compound of formula (I) where  $R^8$  represent hydrogen atom and all other symbols are as defined above with a compound of formula (IVe)



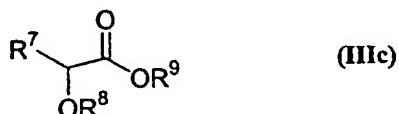
15 where  $R^8$  represents unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl and  $L^2$  is a halogen atom to produce a compound of formula (I) defined above;

f) reacting a compound of the formula (IIIa)



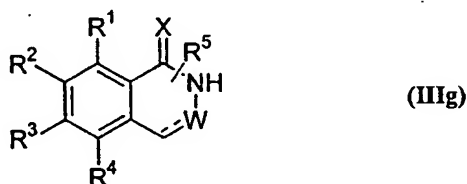


where all symbols are as defined above with a compound of formula (IIIc)

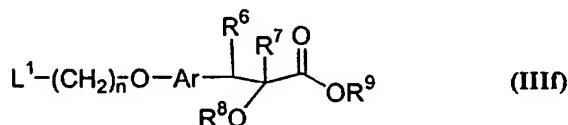


where  $R^7$  is hydrogen and  $R^8$  and  $R^9$  are as defined above to produce a compound of formula (I);

g) reacting a compound of general formula (IIIg)

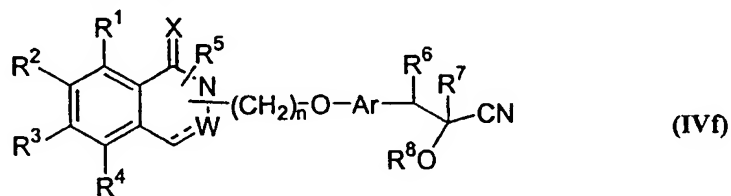


where all symbols are as defined above with a compound of general formula (IIIf)



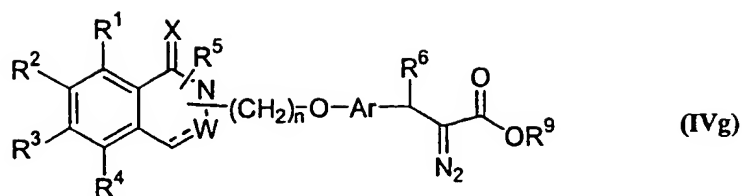
where  $L^1$  is a leaving group and all other symbols are as defined above to produce a compound of formula (I) where all symbols are as defined above, where the linker group  $-(CH_2)_n-O-$  is attached to nitrogen atom;

h) converting a compound of formula (IVf)



where all symbols are as defined above to a compound of formula (I) where all symbols are as defined above;

i) reacting a compound of formula (IVg)

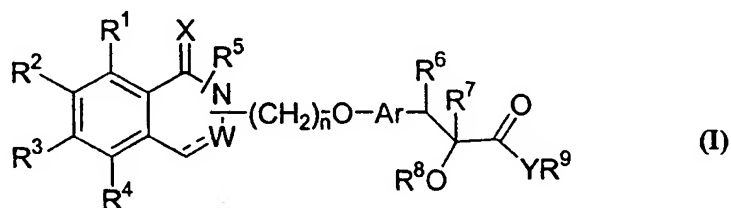


where  $R^9$  is as defined above excluding hydrogen and all other symbols are as defined above with a compound of formula (IVc)



- 5 where  $R^8$  represents unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxyacarbonyl, aryloxyacarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl is as defined above to produce a compound of formula (I) and optionally
- j) converting the compounds of formula (I) obtained in any of the processes
- 10 described above into pharmaceutically acceptable salts or pharmaceutically acceptable solvates.

8. A process for the preparation of compound of formula (I)

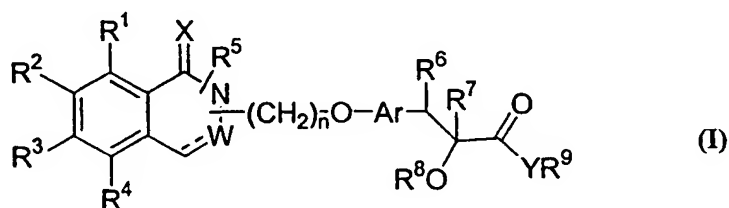


- 15 its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts or its pharmaceutically acceptable solvates, wherein X represents O or S; the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy,
- 20 heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxyacarbonyl, aryloxyacarbonyl, aralkoxyacarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxyacarbonylamino, aralkoxyacarbonylamino, alkoxyacarbonylamino, carboxylic acid or its derivatives or
- 25 sulfonic acid or its derivatives; any two of  $R^1$  to  $R^4$  together with the adjacent carbon

atoms to which they are attached may also form a 5-6 membered cyclic structure containing carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains an oxo group; "----" represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision  
5 that when W represents nitrogen atom, "----" represents a bond or no bond and when W represents an oxygen atom "----" represents no bond; R<sup>5</sup> when present on carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy,  
10 acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkyamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; R<sup>5</sup> when attached to nitrogen atom  
15 represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkyamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl,  
20 alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R<sup>6</sup> represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group R<sup>7</sup>; R<sup>7</sup> represents hydrogen, hydroxy,  
25 alkoxy, halogen, acyl, lower alkyl group or unsubstituted or substituted aralkyl or R<sup>7</sup> forms a bond together with R<sup>6</sup>; R<sup>8</sup> represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl group; R<sup>9</sup> represents hydrogen or unsubstituted or substituted groups  
30 selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; Y represents an oxygen or NR<sup>10</sup>, where R<sup>10</sup> represents hydrogen, alkyl, aryl, hydroxyalkyl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; or R<sup>9</sup> and R<sup>10</sup>

together may form a 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen and the linker group represented by  $-(CH_2)_n-O-$  is attached either through nitrogen atom or through carbon atom, where  $n$  is an integer ranging from 1-4, which comprises :

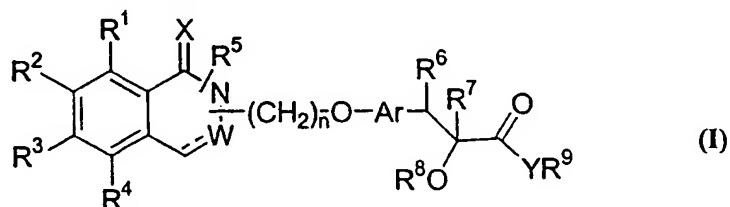
a) reacting a compound of formula (I)



where all symbols are as defined above and Y represents oxygen with an amine of the formula  $NHR^9 R^{10}$  where  $R^9$  and  $R^{10}$  are as defined above and optionally;

b) converting the compounds of formula (I) obtained above into pharmaceutically acceptable salts or pharmaceutically acceptable solvates.

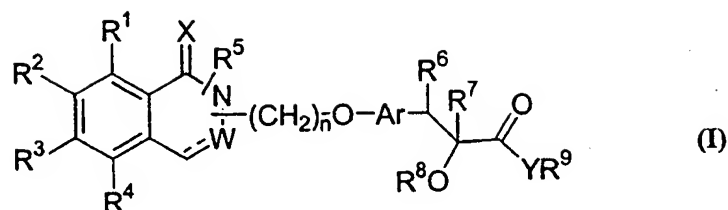
9. A compound of formula (I)



its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts or its pharmaceutically acceptable solvates, wherein X represents O or S; the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of  $R^1$  to  $R^4$  together with the adjacent carbon

atoms to which they are attached may also form a 5-6 membered cyclic structure containing carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains an oxo group; "----" represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that when W represents nitrogen atom, "----" represents a bond or no bond and when W represents an oxygen atom "----" represents no bond; R<sup>5</sup> when present on carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; R<sup>5</sup> when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R<sup>6</sup> together with R<sup>7</sup> represent a bond; R<sup>8</sup> represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl group; R<sup>9</sup> represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; Y represents an oxygen and the linker group represented by  $-(CH_2)_n-O-$  is attached either through nitrogen atom or through carbon atom, where n is an integer ranging from 1-4, prepared according to the process of claim 6.

10. A compound of formula (I)



its its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts or its pharmaceutically acceptable solvates, wherein X represents O or S; the groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and represent

5 hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl,

10 alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of R<sup>1</sup> to R<sup>4</sup> together with the adjacent carbon atoms to which they are attached may also form a 5-6 membered cyclic structure containing carbon atoms which optionally contains one or two heteroatoms selected

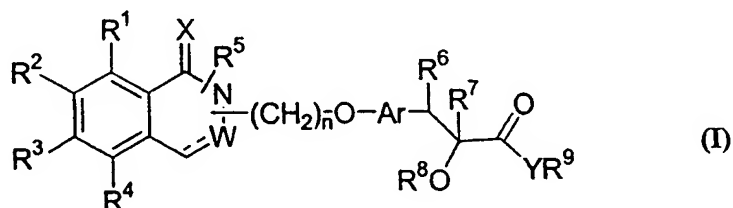
15 from oxygen, nitrogen or sulfur and optionally contains an oxo group; "----" represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that when W represents nitrogen atom, "----" represents a bond or no bond and when W represents an oxygen atom "----" represents no bond; R<sup>5</sup> when present on carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or

20 substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio,

25 aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; R<sup>5</sup> when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy,

heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkyamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxy, aryloxy, aralkoxy, aralkoxy, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R<sup>6</sup> represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or substituted aralkyl group; R<sup>7</sup> represents hydrogen, hydroxy, alkoxy, halogen, acyl, lower alkyl group or unsubstituted or substituted aralkyl; R<sup>8</sup> represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxy, aryloxy, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl group; R<sup>9</sup> represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; Y represents oxygen and the linker group represented by  $-(CH_2)_n-O-$  is attached either through nitrogen atom or through carbon atom, where n is an integer ranging from 1-4, prepared according to the process of claim 7.

11. A process for the preparation of compound of formula (I)



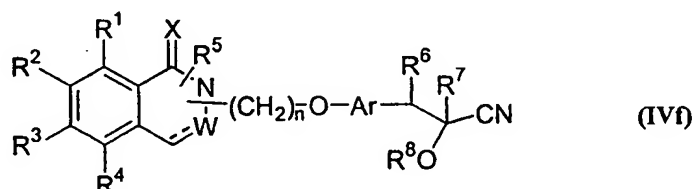
its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts or its pharmaceutically acceptable solvates, wherein X represents O or S; the groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy, aryloxy, aralkoxy, aralkoxy, amino, monoalkylamino, dialkyamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxy, aryloxy, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl group; R<sup>9</sup> represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; Y represents oxygen and the linker group represented by  $-(CH_2)_n-O-$  is attached either through nitrogen atom or through carbon atom, where n is an integer ranging from 1-4, prepared according to the process of claim 7.

aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of  $R^1$  to  $R^4$  together with the adjacent carbon atoms to which they are attached may also form a 5-6 membered cyclic structure containing carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains an oxo group; "----" represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that when W represents nitrogen atom, "----" represents a bond or no bond and when W represents an oxygen atom "----" represents no bond;  $R^5$  when present on carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives;  $R^5$  when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group;  $R^6$  represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group  $R^7$ ;  $R^7$  represents hydrogen, hydroxy, alkoxy, halogen, acyl, lower alkyl group or unsubstituted or substituted aralkyl or  $R^7$  forms a bond together with  $R^6$ ;  $R^8$  represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl group;  $R^9$  represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl



group; Y represents oxygen or  $\text{NR}^{10}$ , where  $\text{R}^{10}$  represents hydrogen, alkyl, aryl, hydroxyalkyl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl group; or  $\text{R}^9$  and  $\text{R}^{10}$  together may form a 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen and the linker group represented by  $-(\text{CH}_2)_n\text{-O-}$  is attached either through nitrogen atom or through carbon atom, where  $n$  is an integer ranging from 1-4, prepared according to the process of claim 8.

12. An intermediate of formula (IVf)

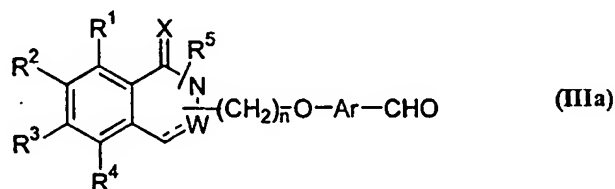


wherein X represents O or S; the groups  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy carbonyl, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxy carbonylamino, aralkoxy carbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; any two of  $\text{R}^1$  to  $\text{R}^4$  together with the adjacent carbon atoms to which they are attached may also form a 5-6 membered cyclic structure containing carbon atoms which optionally contains one or two heteroatoms selected from oxygen, nitrogen or sulfur and optionally contains an oxo group; "----" represents a bond or no bond; W represents an oxygen atom or nitrogen atom, with the provision that when W represents nitrogen atom, "----" represents a bond or no bond and when W represents an oxygen atom "----" represents no bond;  $\text{R}^5$  when present on carbon atom represents hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy carbonyl,

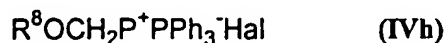
aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxycarbonylamino, aralkoxycarbonylamino, alkoxycarbonylamino, carboxylic acid or its derivatives or sulfonic acid or its derivatives; R<sup>5</sup> when attached to nitrogen atom represents hydrogen, hydroxy, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R<sup>6</sup> represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or substituted aralkyl group or forms a bond together with the adjacent group R<sup>7</sup>; R<sup>7</sup> represents hydrogen, hydroxy, alkoxy, halogen, acyl, lower alkyl group or unsubstituted or substituted aralkyl or R<sup>7</sup> forms a bond together with R<sup>6</sup>; R<sup>8</sup> represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl group; and the linker group represented by -(CH<sub>2</sub>)<sub>n</sub>-O- is attached either through nitrogen atom or through carbon atom, where n is an integer ranging from 1-4

13. A process for the preparation of compound of formula (IVf) defined in claim 12, where R<sup>6</sup> and R<sup>7</sup> represent hydrogen which comprises :

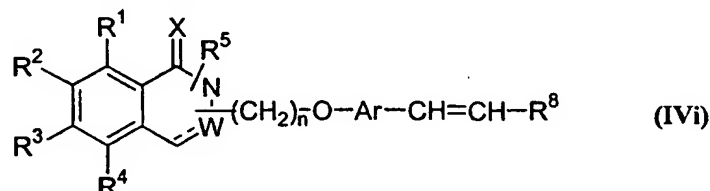
a) reacting a compound of formula (IIIa)



where all symbols are as defined in claim 12 with a compound of formula (IVh)



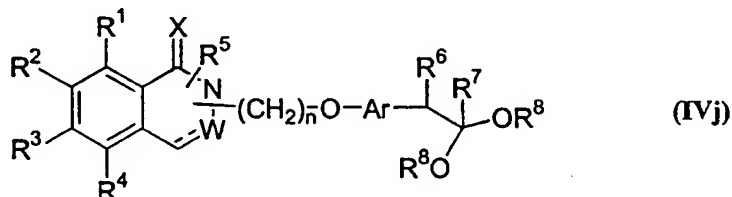
where  $R^8$  represents unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxy carbonyl, aryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl and Hal represents a halogen atom, to yield a compound of formula (IVi)



5

where all symbols are as defined above,

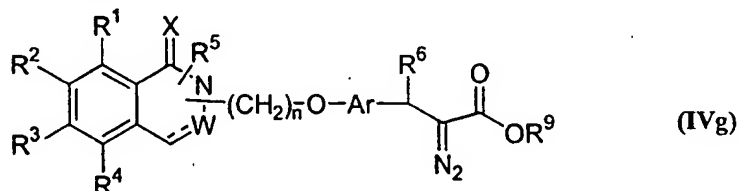
- b) reacting a compound of formula (IVi) with an alcohol of formula  $R^8OH$  where  $R^8$  represents unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxy carbonyl, aryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl to yield a compound of formula (IVj),



where all symbols are as defined above, and

- c) reacting a compound of formula (IVj) obtained above where all symbols are as defined above with trialkylsilyl cyanide to produce a compound of formula (IVf) where all symbols are as defined above.

#### 14. An intermediate of formula (IVg)

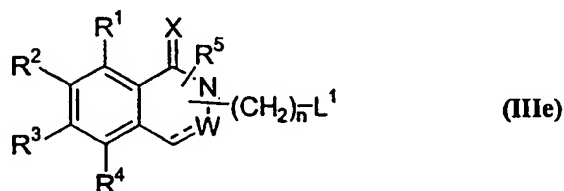


- 20 wherein X represents O or S; the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are the same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or unsubstituted or substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkyloxy, aryl, aryloxy,

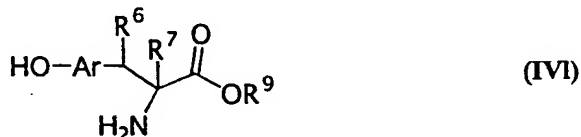
aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy, aryloxy, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, 5 aryloxy, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, alkoxycarbonyl, aryloxy, aryloxy, aralkoxycarbonyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, acylamino, aminoalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, thioalkyl, alkylthio, aryloxy, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaryloxy, heteroaralkyl, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, 15 monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxy, aryloxy, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, carboxylic acid derivatives, or sulfonic acid derivatives; Ar represents unsubstituted or substituted divalent single or fused aromatic or heterocyclic group; R<sup>6</sup> represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl or unsubstituted or 20 substituted aralkyl group; R<sup>9</sup> represents hydrogen or unsubstituted or substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl

group and the linker group represented by  $-(CH_2)_n-O-$  is attached either through nitrogen atom or through carbon atom, where  $n$  is an integer ranging from 1-4,

15. A process for the preparation of compound of formula (IVg) defined in claim 14, which comprises :  
 5 reacting a compound of formula (IIIe)

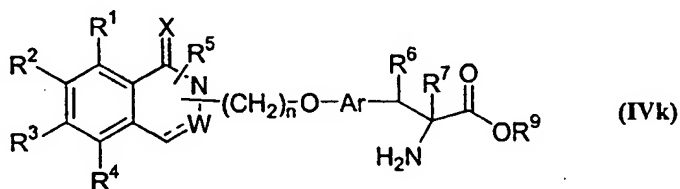


where  $L^1$  is a leaving group and all other symbols are as defined above with a compound of formula (IVl)



10

where  $R^7$  is hydrogen and all symbols are as defined above, to yield a compound of formula (IVk)



where  $R^7$  is hydrogen atom and all other symbols are as defined above,

- 15 b) reacting a compound of formula (IVk) obtained above with an appropriate diazotizing agent.

16. A compound according to claim 1 which is selected from the group consisting of the compounds:

- 20 (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoate ;  
 (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoate ;

- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]  
propanoate ;
- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)]phenyl]  
propanoate ;
- 5 (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)]phenyl]  
propanoate ;
- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)]phenyl]  
propanoate ;
- (±) Ethyl 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]  
10 propanoate ;
- (+) Ethyl 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]  
propanoate ;
- (-) Ethyl 2-hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]  
propanoate ;
- 15 (±) Ethyl 2-methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]  
propanoate ;
- (+) Ethyl 2-methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]  
propanoate ;
- (-) Ethyl 2-methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]  
20 propanoate ;
- (±) Ethyl-2-propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]  
propanoate ;
- (+) Ethyl-2-propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]  
propanoate ;
- 25 (-) Ethyl-2-propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)]phenyl]  
propanoate ;
- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyloxy)]phenyl]  
propanoate ;
- (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyloxy)]phenyl]  
30 propanoate ;

- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 5 (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 10 (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 15 (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 20 (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 25 (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (±) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (+) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 30

- (-) Ethyl 2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoate ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 5 (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 10 (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 15 (±) 2-Hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (+) 2-Hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (-) 2-Hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 20 (±) 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (+) 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 25 (-) 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (±) 2-Propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- (+) 2-Propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its salts ;
- 30



- (-) 2-Propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- (±) Butyl 2-butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 5 (+) Butyl 2-butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (-) Butyl 2-butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (±) 2-Butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- 10 (+) 2-Butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ,
- (-) 2-Butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- 15 (±) Benzyl 2-benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (+) Benzyl 2-benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- (-) Benzyl 2-benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoate ;
- 20 (±) 2-Benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- (+) 2-Benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- 25 (-) 2-Benzyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its salts ;
- 30 (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyl)ethoxy]phenyl]

- propanoic acid and its salts ;  
(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its salts ;  
(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]  
5 propanoic acid and its salts ;  
(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its salts ;  
(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its salts ;  
10 (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its salts ;  
(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its salts ;  
(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]  
15 propanoic acid and its salts ;  
(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its salts ;  
(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its salts ;  
20 (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its salts ;  
(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its salts ;  
(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]  
25 propanoic acid and its salts ;  
(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]  
phenyl]propanoic acid and its salts ;  
(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]  
phenyl]propanoic acid and its salts ;  
30 (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]  
phenyl]propanoic acid and its salts ;

- [2R, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- [2S, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- 5 [(2R),N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-isopropylethyl)propanamide ;
- [(2S),N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-isopropylethyl)propanamide ;
- [2R, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]
- 10 phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- [2S, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- [2R, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- 15 [2S, N(1S)]-2-ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-phthalazinyl)ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid lysine salt ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid
- 20 arginine salt and
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid magnesium salt.
17. A compound according to claim 16, which is selected from :
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid
- 25 and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- 30 (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyl)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;

- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- 5 (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-4-methyl-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (±) 2-Hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (+) 2-Hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- 15 (-) 2-Hydroxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (±) 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- 20 (+) 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (-) 2-Methoxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- 25 (+) 2-Propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- 30

- (+) 2-Propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (-) 2-Propyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (±) 2-Butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (+) 2-Butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (-) 2-Butyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (±) 2-Benzoyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (+) 2-Benzoyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (-) 2-Benzoyloxy-3-[4-[2-(1-oxo-1,2-dihydro-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyloxy)ethoxy]phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-bromo-2-phthalazinyloxy)ethoxy]phenyl]

- propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine,  
5 diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methoxy-2-phthalazinyl)ethoxy]phenyl]  
10 propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]  
15 propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-chloro-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine,  
20 diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]  
25 propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-dimethoxy-2-phthalazinyl)ethoxy]phenyl]  
propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;
- (±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]  
30

propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;

(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]

propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine,

5 diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;

(-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6-methyl-2-phthalazinyl)ethoxy]phenyl]

propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;

(±) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]

10 phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ;

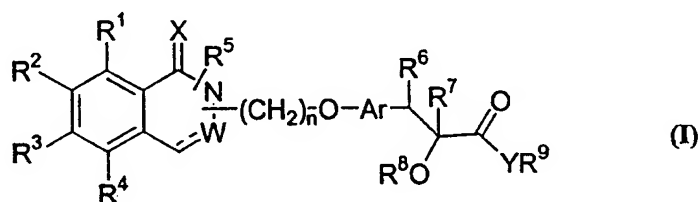
(+) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]

phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts ; and

15 (-) 2-Ethoxy-3-[4-[2-(1-oxo-1,2-dihydro-6,7-(1,3)-dioxolo-2-phthalazinyl)ethoxy]

phenyl]propanoic acid and its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, glycine, diethanolamine, choline, ammonium, substituted ammonium or aluminium salts.

18. A pharmaceutical composition which comprises a compound of formula (I)



20 as defined in claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

19. A pharmaceutical composition as claimed in claim 18, in the form of a tablet, capsule, powder, syrup, solution or suspension.

20. A method of preventing or treating hyperlipidemia, hypercholesteremia,  
25 hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering an effective amount of a compound of formula (I)

as defined in claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claimss 18 or 19 to a patient in need thereof.

21. A method according to claim 20, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

22. A method according to claim 21 for the treatment and /or prophylaxis of disorders related to Syndrome X, which comprises administering an agonist of PPAR $\alpha$  and / or PPAR $\gamma$  of formula (I).

15

23. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising administering an effective amount of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claimss 16 or 17 or a pharmaceutical composition as claimed in claim 18 or 19 to a patient in need thereof.

24. A method of preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering an effective amount of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claim 18 or 19 in combination / concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

25. A method according to claim 24, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension,



- obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.
26. A method according to claim 25 for the treatment and /or prophylaxis of disorders related to Syndrome X, which comprises administering a compound of formula (I) in combination with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol which may be administered together or within such a period as to act synergistically together.
27. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma, which comprises administering a compound of formula (I) claimed in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claim 18 or 19 in combination / concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.
28. Use of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.
29. Use according to claim 28, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive

functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

30. Use of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed  
5 in claim 18 or 19 for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising an effective amount of compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or a pharmaceutical composition as claimed in claims 18 and 19 to a patient in need thereof.

10 31. Use of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claim 18 or 19 in combination/concomitant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol which may be administered together or within such a period as to act synergistically together for  
15 preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism to a patient in need thereof.

32. Use according to claim 31, wherein the disease is type II diabetes, impaired  
20 glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic  
25 ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

33. Use of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed  
30 in claim 18 or 19 in combination/concomitant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids in the plasma.

34. Use of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claim 18 or 19 for preparing a medicament for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.
35. Use according to claim 34, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.
36. Use of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claim 18 or 19 for preparing a medicament for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma.
37. Use of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claim 18 or 19 for preparing a medicament in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for preventing or treating hypelipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.
38. Use according to claim 37, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic

ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

39. Use of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11  
5 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claim 18 or 19 for preparing a medicament in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids in the plasma.
- 10 40. A medicine for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering an effective amount of a compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or  
15 17 or a pharmaceutical composition as claimed in claim 17 or 18.
41. A medicine according to claim 40, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis,  
20 glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.
- 25 42. A medicine for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising an effective amount of compound of formula (I) as defined in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claim 17 or 18.
43. A medicine for preventing or treating hyperlipidemia, hypercholesteremia,  
30 hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising a compound of formula (I) as defined in any one of claims 1 to

5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claim 18 or 19 and HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.

44. A medicine according to claim 43, wherein the disease is type II diabetes,  
5 impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic  
10 ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

45. A medicine for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma, which comprises a compound of formula (I)  
15 claimed in any one of claims 1 to 5, 9 to 11 or a compound as claimed in claim 16 or 17 or a pharmaceutical composition as claimed in claim 18 or 19 and HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.

# INTERNATIONAL SEARCH REPORT

International Application No

PC1/IB 99/00131

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D237/32 C07D491/04 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 91 19702 A (PFIZER) 26 December 1991 cited in the application see page 1 - page 23; claims; example 1	1,9,18, 19,28-45
E	EP 0 903 343 A (SSP CO) 24 March 1999  see page 1 - page 17; claims; examples 1,11,17; tables 1-18	1-11,18, 19,28-45



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 May 1999

Date of mailing of the international search report

01/06/1999

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

national application No.

PCT/IB 99/00131

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 20-27  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 20-27  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 99/00131

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